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NORTHERN DISTRICT OF CALIFORNIA

United States District Court
Northern District of California

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

TAKEDA PHARMACEUTICAL CO., LTD, et al., Plaintiffs, v. HANDA PHARMACEUTICALS, LLC, AND PAR PHARMACEUTICALS, Defendants.	**FINDINGS OF FACT AND CONCLUSIONS OF LAW** [redacted] Case No. C-11-00840 JCS
TAKEDA PHARMACEUTICAL CO., LTD, et al., Plaintiffs, v. TWI PHARMACEUTICALS, INC., Defendant.	Case No. C-11-01609 JCS
TAKEDA PHARMACEUTICAL CO., LTD, et al., Plaintiffs, v. IMPAX LABORATORIES, INC., Defendant.	Case No. C-11-01610 JCS

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I. INTRODUCTION

Takeda Pharmaceutical Co., Ltd., Takeda Pharmaceuticals North America, Inc., Takeda Pharmaceuticals LLC, and Takeda Pharmaceuticals America, Inc. (hereinafter referred to collectively as "Takeda") initiated this action under the Drug Price Competition and Patent Term Restoration Act of 1984 (the "Hatch-Waxman Act"), 35 U.S.C. § 271(e)(2)(A), in response to the filing of Abbreviated New Drug Applications ("ANDA") by Handa Pharmaceuticals, LLC ("Handa"), Impax Laboratories, Inc. ("Impax"), and TWi Pharmaceuticals, Inc. ("TWi"). Takeda claims the proposed ANDA products infringe upon its existing patents. Takeda also asserts infringement under 35 U.S.C. §271(a) and the Declaratory Judgment Act, 28 U.S.C. §§ 2201, 2202, as to Defendant TWi only.

At the outset of the three related cases, Takeda asserted Defendants' ANDA products infringed the following patents: 1) U.S. Patent No. 6,462,058 ("the '058 Patent"); 2) U.S. Patent No. 6,664,276 ("the '276 Patent"); 3) U.S. Patent No. 6,939,971 ("the '971 Patent"); 4) U.S. Patent No. 7,737,282 ("the '282 Patent"); 5) U.S. Patent No. 7,285,668 ("the '668 Patent") and 6) U.S. Patent No. 7,790,755 ("the '755 Patent"). Defendants, in turn, asserted counterclaims seeking declaratory judgment of noninfringement and invalidity as to the asserted patents.

On April 11, 2012, the Court issued its Claim Construction Order construing disputed claim terms found in one or more of the asserted patents. *See* Claim Construction Order [Case No. 3:11-cv-840, D.N. 106]. The case was subsequently narrowed to eleven asserted claims from the '755, '282, '058, '276, and '971 Patents. In particular, Takeda asserted that: 1) the ANDA submitted by Defendants Handa and Par Pharmaceuticals infringes claims 2, 4, and 6 of the '755 Patent, claims 1 and 2 of the '282 Patent and claims 2 and 3 of the '276 Patent; 2) the ANDA submitted by Defendant TWi infringes claims 2 and 4 of the '755 Patent and claims 1 and 2 of the '282 Patent; and 3) the ANDA submitted by Impax infringes claims 2, 4 and 6 of the '755 Patent, claims 1 and 3 of the '058 Patent, claims 2 and 3 of the '276 Patent, and claims 6 and 7 of the '971 Patent.

Following briefing and submission of evidentiary material and argument, on April 8, 2013, the Court entered a summary judgment order in each of the three related cases. *See* Handa

Summary Judgment Order [Case No. 3:11-cv-840, D.N. 265] ("Handa Summary Judgment Order"); TWi Summary Judgment Order [Case No. 3:11-cv-1609, D.N. 235] ("TWi Summary Judgment Order"); Impax Summary Judgment Order [Case No. 3:11-cv-1610, D.N. 241] ("Impax Summary Judgment Order"). The Court granted summary judgment of noninfringement of the '755 Patent in favor of all Defendants. *See* Handa Summary Judgment Order at 49-51; TWi Summary Judgment Order at 47-51; Impax Summary Judgment Order at 49-51. The Court granted summary judgment of infringement of the '282 Patent by Handa and TWi and denied Handa and TWi's motions as to invalidity of the '282 Patent on grounds of anticipation. *See* Handa Summary Judgment Order at 39-48; TWi Summary Judgment Order at 39-45. The Court also granted Takeda's motion for summary judgment of infringement of the '058, '276, and '971 Patents by Impax and denied Impax's cross-motion as to noninfringement of claims 1 and 3 of the '058 Patent and claim 7 of the '971 Patent. *See* Impax Summary Judgment Order at 47-49. The Court rejected Impax's claim that the '971 Patent lacks an adequate written description to support claims 6 and 7 of that patent. *Id.* The Court denied Handa's motion of noninfringement as to the '276 Patent, finding there to be a triable issue of fact. *See* Handa Summary Judgment Order at 48-49.

The Court held a six-day bench trial beginning on June 5, 2013 and concluding on June 12, 2013. The issues that remained at trial were as follows: 1) does Handa's ANDA product infringe the '276 Patent because it contains crystalline dexlansoprazole; 2) are claims 2 and 3 of the '276 Patent invalid because they are obvious in view of the prior art; 3) are claims 1 and 2 of the '282 Patent invalid on the basis that they are anticipated, obvious, or lack sufficient written description; 4) are claims 1 and 3 of the '058 Patent invalid because they are obvious; 5) are claims 6 and 7 of the '971 Patent invalid because they are obvious; 6) do the Takeda entities in the United States – Takeda Pharmaceuticals North America, Inc. (now Takeda Pharmaceuticals U.S.A., Inc.), Takeda Pharmaceuticals LLC and Takeda Pharmaceuticals America, Inc. – have standing to assert infringement of the '282 Patent against TWi; and 7) is there a real and immediate controversy sufficient to establish jurisdiction under the Declaratory Judgment Act as to Takeda's infringement claim under § 271(a), asserted against TWi. The parties filed post-trial briefs on June 28, 2013.

Pursuant to Federal Rule of Civil Procedure 52(a), the Court makes the following findings of fact and conclusions of law. [1]

II. FINDINGS OF FACT

A. The Parties

1. Takeda Pharmaceutical Company Limited ("TPC") is a Japanese corporation with its principal place of business at 1-1, Doshomachi 4-chome, Chuo-ku, Osaka, Japan. TPC is the owner of record and assignee of the '058, '276, '971 and '282 Patents.

2. Takeda Pharmaceuticals North America, Inc. ("TPNA") is a Delaware corporation with its principal place of business at One Takeda Parkway, Deerfield, IL 60015. TPNA recently changed its name to Takeda Pharmaceuticals U.S.A., Inc. TPNA is the registered holder of approved New Drug Application No. 22-287 for Dexilant.

3. Takeda Pharmaceuticals LLC ("Takeda LLC") is a Delaware limited liability company, having a principal place of business at One Takeda Parkway, Deerfield, IL 60015.

4. Takeda Pharmaceuticals America, Inc. ("TPA") is a Delaware corporation, having a principal place of business at One Takeda Parkway, Deerfield, IL 60015.

5. Handa Pharmaceuticals, LLC is a limited liability company organized under the laws of California with its principal place of business at 39465 Paseo Padre Parkway, Suite 2600, Fremont, CA 94538.

6. Par Pharmaceutical, Inc. is a corporation organized under the laws of Delaware with its principal place of business at 300 Tice Boulevard, Woodcliff Lake, NJ 07677.

7. Handa submitted ANDA No. 202-294 to the U.S. Food and Drug Administration ("FDA"), seeking approval for the manufacture, use, or sale of 60-mg dexlansoprazole capsules. Subsequently, Handa and Par entered into an exclusive acquisition and license agreement concerning ANDA No. 202-294, effective March 12, 2012, and Par is now the owner of that ANDA. [Joint Statement of Undisputed Facts for Takeda's Motion for Summary Judgment of

[1] Any Findings of Fact that constitute Conclusions of Law shall be deemed to have been found by the Court as a matter of law. Conversely, any Conclusions of Law that constitute Findings of Fact shall be deemed to have been found by the Court as a matter of fact.

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Infringement of the '282 Patent ("JSUF (Takeda Motion)") ¶¶ 5-6] Hereinafter, the Court refers to Handa and Par collectively as "Handa."

8. Defendant TWi Pharmaceuticals, Inc. is a corporation organized under the laws of Taiwan with its principal place of business at 4Fl., No. 41, Lane 221, Kang Chien Rd., Nei Hu Dist., Tai Pei 114 Taiwan. [Case No. 3:11-cv-1609, D.N. 22].

9. TWi is the owner of ANDA No. 202-666, which has been submitted to the FDA and which seeks approval to market dexlansoprazole delayed-release capsules in 30-mg and 60-mg dosage forms.

10. Defendant Impax Laboratories, Inc. is a corporation organized under the laws of Delaware with its principal place of business at 30831 Huntwood Ave., Hayward, CA 94544. [Case No. 3:11-cv-1610, D.N. 14].

11. Impax is the owner of ANDA No. 202-576, which has been submitted to the FDA and which seeks approval for the manufacture, use, or sale of dexlansoprazole delayed-release capsules in 30-mg and 60-mg dosage forms.

B. Background of Technology

1. Crystals

12. Crystals are solids in which the atoms (or molecules) are arranged in a periodic repeating pattern that extends in three dimensions. *See* Trial Transcript ("Trial Tr.") (Myerson Direct) 173:7-10. Solids that are not crystalline and have no long range order (meaning that their constituent molecules are similarly oriented for no more than a few molecules) – such as glass – are said to be amorphous. Amorphous solids are generally less chemically stable than crystalline solids of the same compound. *See id.* (Myerson Direct) 175:7-21.

13. The internal structure (called the crystal structure or crystalline lattice) of molecular crystals is determined by the position of the molecules relative to each other and extending in three dimensions. *See id.* (Myerson Direct) 173:7-18.

14. A crystal lattice can be characterized in terms of three spatial dimensions – a, b, and c – and three angles – alpha, beta, and gamma. These lengths and angles are known as lattice parameters and a single cell constructed using these parameters is called the unit cell. The

dimensions of the unit cell of a crystal (making up a crystal's internal architecture) are unique and can be used to distinguish one crystalline form of a molecule from another crystalline form of the same molecule. *See id.* (Myerson Direct) 173:19-174:1; *id.* (Atwood Direct) 798:20-799:16.

2. X-Ray Powder Diffraction Analysis

15. X-ray diffraction is a technique used to identify crystals and to determine crystal structure. Crystal structure can be determined using single crystal x-ray diffraction. In this method a single crystal with dimensions of at least 0.1 mm in all dimensions is prepared. This crystal is then rotated and exposed to x-rays. The resulting data can be analyzed to determine lattice type, unit cell dimensions and the location of each atom in the crystal relative to the other atoms, thus enabling a three dimensional understanding of the crystal structure. *See* Trial Tr. (Myerson Direct) 176:4-17.

16. Another type of x-ray diffraction, known as x-ray powder diffraction ("XRPD"), is also used to identify crystals. XRPD analyzes a small amount of ground crystalline powder rather than a single crystal and produces a pattern of peaks that acts as a signature or fingerprint for the substance being analyzed. *See id.* (Myerson Direct) 176:18-178:3.

17. In XRPD, a sample of the material of interest is first lightly ground into a fine powder. XRPD relies on the fact that the array of tiny crystals in the powder sample, randomly arranged, will present all possible lattice planes for reflection of an incident beam of x-rays. When x-rays are directed at such a crystalline solid, an observable pattern is produced because the distances between atoms in a crystal are of a length similar to the x-ray wavelength. The relationship between the wavelength of the x-rays and the spacing between atoms in a crystal is known as Bragg's law: $n\lambda = 2d \sin \theta$, where λ is the wavelength of the incident x-rays, d is the interplanar spacing in the crystal and θ is the angle of incident x-rays on the crystal. *Id.*

18. XRPD data is often reported in terms of d-spacings and Bragg angles (known as "2θ" or "two-theta" values) as well as relative intensities (which for any given peak is shown as a percentage of the intensity of the maximum peak). The two-theta values are a function of the wavelength of the x-rays used. The d-spacings are the distances between adjacent crystal planes in the lattice. Because these d-spacings are a property of the crystalline solid, unlike two-theta

values they are invariant. For any x-ray wavelength, d-spacing data can be used to calculate two-theta angles, and vice versa. *Id.* (Myerson Direct) 178:4-15.

19. The x-ray pattern (particularly the location of the peaks) acts as a "fingerprint" for a given crystal form of a particular compound and a selection of peaks from an XRPD pattern can be used to identify a compound and its crystalline phase. *Id.* (Myerson Direct) 177:23-178:3.

20. XRPD is commonly used to characterize the active ingredient in a drug product. *Id.* (Myerson Direct) 185:2-5.

3. Polymorphs, Solvates and Hydrates

21. It is possible for a given chemical compound to crystallize into more than one distinct crystal structure. This ability is called polymorphism. Different polymorphs of the same compound can be as different from one another in terms of their properties as different compounds. Trial Tr. (Myerson Direct) 183:2-11.

22. A solvate is a crystal in which solvent is part of the crystalline structure. A solvate in which the solvent is water is usually referred to as a hydrate. *Id.* (Myerson Direct) 183: 13-17. Approximately fifty percent of pharmaceutical compounds are either polymorphic or have solvates or hydrates. *Id.* (Myerson Direct) 184: 5-9.

23. Polymorphs may convert from one form to another during manufacture and storage. Typically that conversion would be from a less stable form to a more stable form. At a given temperature, for example, one polymorph is the thermodynamically stable form. This does not mean that other polymorphs cannot exist under those conditions; it means only that one polymorph is stable and any others present can convert to the stable polymorphic form. For example, an amorphous form can convert to a crystalline form because an amorphous form is generally less stable than a crystalline form. *See id.* (Myerson Direct) 184: 10-21.

4. Crystallization and the Formation of Polymorphs

24. The process by which crystals are formed is called crystallization. Crystallization of molecules has long been known, and crystallization of pharmaceutical compounds has been a common practice in the pharmaceutical industry and in academic research laboratories for decades. Trial Tr. (Genck Direct) 715:8-10; *id.* (Atwood Direct) 964:22-965:6. The general

technique of crystallization is taught to undergraduate students as part of their training and is used routinely by chemists in the preparation and purification of organic compounds. *Id.* (Atwood Direct) 964:6-21.

25. Many methods of crystallization exist. Crystallization from solution is a common crystallization method in which a solid material (known as the solute) is first dissolved in a liquid (known as the solvent). *Id.* (Atwood Direct) 934:15-936:9.

26. Crystallization from solution is the result of three successive processes: (1) supersaturation of the solution, which means that more than the thermodynamically stable amount of a compound is in solution; (2) formation of crystal nuclei; and (3) crystal growth around the nuclei. Supersaturation can be achieved by cooling the solution, evaporating the solvent, changing the pH of the solution, or introducing a solvent into the solution in which the compound is less soluble, or a combination of the foregoing. As a result of these steps, the solution becomes supersaturated. *Id.* (Atwood Direct) 934:15-939:8.

27. Supersaturation itself is insufficient to cause crystal formation; the crystal embryos must form by collision of molecules of solute in the solution, or sometimes by addition of seed crystals. If the molecules are not oriented properly so as to crystallize, or if the compound is a liquid at room temperature, then supersaturation will not result in a crystal. *Id.* (Atwood Direct) 938:20-939:8.

28. Once a newly synthesized compound has been crystallized, subsequent crystallizations are generally easier because of the presence of suitable seeds to serve as the site of nucleation. *Id.* (Atwood Direct) 972:9-973:8; *Id.* (Genck Direct) 723:14-724:7. Seeding may be unintentional or intentional. Intentional seeding involves adding small crystals or crystallites (small, often microscopic crystals) to a supersaturated solution to encourage nucleation of the desired crystal, thereby speeding up the crystallization process. *Id.* (Genck Direct) 723:15-724:1; *id.* (Atwood Direct) 972:1-8. Unintentional seeding sometimes occurs in laboratories where compounds are crystallized because the working atmosphere may become contaminated with seeds of the particular material, which promotes subsequent crystallization. *Id.* (Atwood Direct) 972:13-973:9.

29. Organic molecules are generally more difficult to crystallize because there are several

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possible ways for the pendant groups on the outside of the molecule to arrange themselves in three-dimensional space. *Id.* (Atwood Direct) 941:4-24.

5. Column Chromatography

30. Chromatography is a technique designed to separate molecules in a sample. Column chromatography is a technique that carries out this separation using a column that is packed with some kind of solid matrix, such as silica-gel beads, that has an affinity for the compound of interest. Trial Tr. (Atwood Direct) 952:24-955:20.

31. This technique involves applying a mixture of the sample in solution to the top of the column. Large amounts of a liquid solvent are then added, into which the sample dissolves. The solvent containing the samples (called the mobile phase) then flows through the column, typically under high pressure. Different types of molecules in the sample may interact with the silica-gel matrix as they travel through the column, and if they do interact they will travel more slowly through the column. Other molecules that do not interact with the matrix will travel through the column more quickly. These different rates of travel allow the molecules to be separated, because they emerge from the bottom of the column at different times. The separated materials that come off the column will still be in the mobile phase (solvent). *See id.*

6. Enantiomers and Racemates

32. "Enantiomers" are non-superimposable mirror images of a given compound, just as a person's left and right hands are non-superimposable images of each other. They are designated by their handedness as right (R) or left (S), or by the direction they rotate a plane of polarized light. *See* Trial Tr. (Rogers Direct) 482:14-20.

33. Substances that can rotate polarized light are said to be optically active because they interact with light and can rotate plane-polarized light. *Id.* (Atwood Cross) 1057:19-20.

34. Enantiomers that rotate plane-polarized light clockwise are said to be dextrorotatory or (+). Those that rotate plane-polarized light counterclockwise are called levorotatory or (–). *Id.* (Atwood Cross) 1057:19-20.

35. Racemates are mixtures of both the R-enantiomer and the S-enantiomer; racemates can be separated using various techniques, including chromatography. *Id.* (Rogers Direct) 482: 21-22.

36. "Enantiomeric excess" or "e.e." is a measure of the optical purity of an enantiomer. The optical purity of an R-enantiomer is obtained by subtracting the amount of S-enantiomer in a given compound from the amount of R-enantiomer in that compound. *Id.* (Kamiyama Direct) 86: 4 - 87: 3.

7. Takeda's Inventions

37. The patents-in-suit claim amorphous and crystalline forms of dexlansoprazole, a compound used to treat gastroesophageal reflux disease ("GERD"). The '282 Patent claims an amorphous form of dexlansoprazole (hereinafter, "Amorphous Form Patent"). The, '276, '058 and '971 Patents relate to crystalline forms of dexlansoprazole (hereinafter, "Crystal Form Patents").

38. Dexlansoprazole is a chemical compound known as (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole. It is the R-enantiomer of lansoprazole.

39. Lansoprazole is the active pharmaceutical ingredient ("API") in the drug Prevacid®, which Takeda began marketing in 1995. Lansoprazole is a racemic mixture of the enantiomers dexlansoprazole (the right, R+, or (+) enantiomer) and levolansoprazole (the left, S-, or (-) enantiomer). This means that lansoprazole contains 50% of each of the two enantiomers with alternating right-handed and left-handed molecules intermixed. *See* Trial Tr. (Atwood Direct) 968:17-18.

40. The Amorphous and Crystal-Form Patents grew out of the work of Takeda scientists Akira Fujishima, Isao Aoki, and Keiji Kamiyama, who sought to isolate stable solid forms of dexlansoprazole. These four patents are part of the same patent family and claim priority to a Japanese patent application filed June 17, 1999. TX 0001 ('058 Patent); TX 0002 ('276 Patent); TX 1054 ('971 Patent); TX 1055 ('282 Patent). All have essentially the same specification.

a. Crystalline Dexlansoprazole

41. In May 1999, Dr. Kamiyama began working on the crystallization of the separate enantiomers of lansoprazole – the PPI used in Takeda's Prevacid® drug – in order to protect Takeda's market in the face of impending generic competition resulting from the expiration of

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Takeda's first patent for lansoprazole. Trial Tr. 82:20-25 (Kamiyama Direct); *id.* (Kamiyama Cross) 122:6-24; TX 0306A-0036 (TAK-390MR2[2] New Employee Training) (goal of crystallization of both enantiomers was given "top priority" in light of lansoprazole patent expiration). Dr. Kamiyama began his efforts by obtaining samples of the amorphous solids of (R+)-lansoprazole and (S-)-lansoprazole from Takeda's Production Technology Division. *See* Trial Tr. (Kamiyama Direct) 85:3-86:3; TX 0306A-0036 (TAK-390MR New Employee Training, describing research on TAK390).

42. Dr. Kamiyama started with a little over a gram of dexlansoprazole, which he divided into 10 smaller samples of approximately 100 milligrams each in order to conduct crystallization experiments. *See id.* (Kamiyama Direct) 85:3-86:3; TX 0306A-0037. Dr. Kamiyama did so because he did not know if he would be successful in obtaining a crystal of dexlansoprazole and wanted enough samples to allow him to conduct multiple crystallization experiments. Trial Tr. (Kamiyama Direct) 85: 11-13; TX 0306A-0037.

43. Dr. Kamiyama's first attempts to crystallize dexlansoprazole using solvents included an attempt using ethyl acetate with hexane and an attempt using ethanol with hexane. These attempts failed to produce crystals. *See* Trial Tr. (Kamiyama Direct) 88:11-23, 110:16-21. Dr. Kamiyama also later failed to obtain dexlansoprazole crystals using tetrahydrofuran ("THF") and methanol as solvents. *See id.* (Kamiyama Direct) 110:22-11:5.

44. Dr. Kamiyama was able to crystallize dexlansoprazole after one or two days of experiments. *Id.* (Kamiyama Cross) 115: 16-24. (Kamiyama Direct) 91:1-92:22.

i. Example 1

45. Dr. Kamiyama's first successful crystallization is described in Example 1 of the Amorphous and Crystal-Form Patents. Trial Tr. (Kamiyama Direct) 91:1-92:22. The method that Dr. Kamiyama used to successfully crystallize dexlansoprazole involved several steps. First, he dissolved a small amount of amorphous solid of (R+)-lansoprazole in acetonitrile. Next, he gradually evaporated the solution at room temperature while blowing a nitrogen stream over the

[2] Takeda refers to dexlansoprazole as TAK390. Trial Tr. (Kamiyama Direct) 138: 24-25.

surface of the solution. *See* Trial Tr. (Kamiyama Direct) 87:14-88:6, 92:3-22; TX 0001-0006 ('058 Patent) at col.10, ll.25-42 (Example 1). The use of a nitrogen stream encouraged evaporation of solvent and cooling of the solution, thereby promoting crystallization. Trial Tr. (Kamiyama Direct) 89:8-16; *id.* (Genck Direct) 718:8-719:8 (blowing a nitrogen stream across the surface of the solution leads to evaporation and cooling).

46. After a crystal began to form, Dr. Kamiyama added diethyl ether to the solution and stoppered the container at room temperature. *Id.* (Kamiyama Direct) 87:14-88:66, 92:3-22; TX 0001-0006 ('058 Patent) at col.10, ll.25-42 (Example 1). This method yielded a small quantity of the anhydrous crystal of dexlansoprazole described in claim 1 of the '058 Patent (38 mg). *See* TX 0001-0006 ('058 Patent) at col.10, ll.25-42 (Example 1).

ii. Example 3

47. Dr. Kamiyama attempted additional crystallization techniques to obtain crystals of dexlansoprazole. *See* Trial Tr. (Kamiyama Direct) 96:14-19, 97:11-17. One of those techniques resulted in the sesquihydrate (1.5 hydrate) crystal described in Example 3 of the '058 Patent. *See id.* (Kamiyama Direct) 96:14-97:2. Dr. Kamiyama testified credibly that he did not expect to obtain a sesquihydrate crystal. *Id.* (Kamiyama Direct) 97: 18-20.

48. In Example 3, 100 mg of amorphous solid dexlansoprazole from Reference Example 1 was dissolved in ethanol and water. TX 0001-0007 ('058 Patent) at col.12, ll.11-24. This failed to result in crystallization. Trial Tr. (Kamiyama Direct) 97:14-98:3. A seed from the anhydrous crystal disclosed in Example 1 of the '058 Patent was then placed in the solution, and the solution was kept standing at room temperature for an hour. TX 0001-0007 ('058 Patent) at col.12, ll. 18-20. This seeding caused crystallization to occur, although the crystal formed was different from that of the seed crystal. *See id.* Precipitated crystals were collected by filtration, washed, and dried to yield 96 mg of the sesquihydrate crystal of dexlansoprazole. *Id.* at col.12, ll. 20-24.

49. X-ray powder diffraction data for the 1.5 hydrate crystal is shown in Table 3 of the '058 Patent. *Id.* at col.12, ll.29-44.

iii. Example 2

50. Dr. Kamiyama later attempted to manufacture a greater quantity of the anhydrous crystal

of dexlansoprazole for use in an animal study described in Experimental Example 1 of the Crystal-Form Patents as well as other experiments. *See* Trial Tr. (Kamiyama Direct) 100:23-101:17, 108:11-22.

51. He succeeded by taking the approach described in Example 2 of the '058 Patent, using the amorphous solid dexlansoprazole from Reference Example 2 as starting material. TX 0001 ('058 Patent) at TX 0001-0007, col.11, ll.11-43 (Example 2); *see also* Trial Tr. (Kamiyama Direct) 103:25-104:19. This crystallization experiment involved several steps. *Id.*

52. In the first step, Dr. Kamiyama obtained a sesquihydrate crystal from the amorphous form using the following procedure: First, 9.17 grams of the amorphous solid (98.3% e.e.) were dissolved under heating in acetone and water. TX 0001 ('058 Patent) at TX 0001-0007, col.11, ll.16-19. The resulting solution was kept standing at room temperature overnight. Then water was added and the mixture was subjected to ultrasonication. *See id.* at col.11, ll.20-22. This process resulted in a solid, which was collected by filtration, washed, and dried to yield 9.10 grams of the sesquihydrate crystal of dexlansoprazole. *See id.* at col.11, ll. 22-25; Trial Tr. (Kamiyama Direct) 103:25-104:6, 104:20-25.

53. In the second step, Dr. Kamiyama obtained an anhydrate crystal from the sesquihydrate crystals using the following procedure: 9.00 grams of the sesquihydrate crystals were dissolved in acetone and filtered. TX 0001 ('058 Patent) at TX 0001-0007, col.11, ll.25-27. Diisopropylether was added to the filtrate and a seed from the anhydrous crystal disclosed in Example 1 was added to the mixture, which was kept standing at room temperature overnight. *Id.*, col.11, ll.27-29; Trial Tr. (Kamiyama Direct) 105:12-19. The resulting crystals were collected, washed, and dried to yield 7.85 grams of the anhydrous crystal of dexlansoprazole (optical purity 99.8% e.e.). TX 0001 ('058 Patent) at TX 0001-0007, col.11, ll.29-32; TX 0502 & TX 0502A (Kamiyama laboratory notebook and partial English translation) at TX 0502-0013 & TX 0502A-0013; Trial Tr. (Kamiyama Direct) 103:25-104:15, 105:1-5, 108:23-109:21.

54. In the third step, Dr. Kamiyama obtained hydrate crystal from anhydrate crystal using the following procedure: 7.80 grams of these anhydrous crystals were dissolved under heating in acetone and water, and this solution was kept standing at room temperature for an hour. TX 0001

('058 Patent) at TX 0001-0007, col.11, ll.32-34. A precipitated solid was collected by filtration, washed, and dried to yield 3.88 grams of the sesquihydrate crystal of dexlansoprazole. *Id.*, col.11, ll.35-37; Trial Tr. (Kamiyama Direct) 103:25-104:15, 105:6-8. The optical purity of this sesquihydrate crystal (99.8% e.e.) was higher than that of the anhydrate crystal in step 2 above. *See* TX 0502 & TX 0502A (Kamiyama laboratory notebook and partial English translation) at TX 0502-0013 & TX 0502A-0013; Trial Tr. (Kamiyama Direct) 108:23-109:21.

55. In the fourth and final step, Dr. Kamiyama obtained an anhydrate crystal from hydrate crystal using the following procedure: the entire amount of sesquihydrate crystals obtained in step 3 above were dissolved under heating in acetone and diisopropyl ether, and the solution was kept standing at room temperature for 30 minutes. TX 0001 ('058 Patent) at TX 0001-0007, col.11, ll.37-40. Precipitated crystals were collected by filtration, washed, and dried to yield 3.40 grams of the anhydrate crystal of dexlansoprazole (99.8% e.e.). *Id.*, col.11, 30-44; Trial Tr. (Kamiyama Direct) 103:25-104:15, 105:9-11.

56. Example 2 thus sets forth additional techniques for obtaining sesquihydrate and anhydrate crystals of dexlansoprazole. Although only the second step involved the intentional use of a seed crystal, the crystallization was performed in the same lab in which the sesquihydrate crystal was first obtained in Example 3. Moreover, the second crystallization of the anhydrous crystal occurred after one such crystallization had already been performed in Example 2. Accordingly, the crystallizations described in Example 2 may have been facilitated by both intentional and unintentional seeding.

57. Table 2 reports the x-ray powder diffraction data for the resulting anhydrous crystal of dexlansoprazole. The d-spacings listed in Table 2 correspond to the d-spacings listed in claim 1 of the '058 Patent, and are reported as 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom. *See* TX 0001 ('058 Patent) at TX 0001-0007, col.11, tbl. 2, TX 0001-0008, col.14, ll.25-30 (claim 1).

iv. Reference Example 4

58. Reference Example 4 describes a series of experiments in which Takeda generated the anhydrous crystal of dexlansoprazole described in Example 2 on a much larger production scale.

TX 0001-0005 to -0006 ('058 Patent), col.8, l.31 to col.10, l.23 (Reference Example 4.

59. The first step was the asymmetric oxidation of 4.5 kilograms of lansoprazole derivative, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]thio] benzimidazole. This reaction resulted in dexlansoprazole in the reaction liquor, which was then crystallized and recrystallized multiple times to improve its chemical and optical purity. TX0001-0005, col.8, 11.35-53.

60. In step two, four solvents in succession were added to the organic layer resulting from the asymmetric oxidation reaction to yield a highly pure crystal (100% e.e.) of dexlansoprazole with d-spacings at 5.85, 4.70, 4.35, 3.66, and 3.48 Angstrom. TX 0001-0005 to -0006 ('058 Patent) at col.8, l.53 to col.9, ll.8.

61. In step three, the crystal obtained in step two was suspended in acetone and subjected to additional steps that resulted in another highly pure crystal (100% e.e.) of dexlansoprazole with d-spacings at 8.33, 6.63, 5.86, and 4.82 Angstrom. TX 0001-0006 ('058 Patent), col.9, ll.9-26.

62. In step four, the crystal obtained in step three was dissolved in ethyl acetate and water and a trace amount of insoluble material in the organic layer was removed. Triethylamine was added to the remaining ethyl acetate-water mixture, and the mixture was concentrated under reduced pressure. Methanol and aqueous ammonia and t-butyl ether were added at 50° C, and additional separations were performed. These separations resulted in a concentrate that was dissolved in acetone, concentrated, dissolved in more acetone, and then added drop by drop into a mixture of acetone and water. This resulted in a highly pure crystal (100% e.e.) of dexlansoprazole with d-spacings at 8.33, 6.63, 5.86, and 4.82 Angstrom. *Id.* at col.9, ll.27-65.

63. In step five, the crystal obtained in step four was dissolved in ethyl acetate, and the water layer was separated from the organic layer. The resulting organic layer was then concentrated under reduced pressure, and ethyl acetate and activated charcoal were added. After stirring, the activated charcoal was removed by filtration. The filtrate was concentrated under reduced pressure and then heptane was added in a dropwise fashion (drop by drop) at 40° C. The resulting crystal was separated and washed with ethyl acetate-heptane at 40° C. *Id.* at col.9, l.66 to col.10, l.12.

64. This process yielded 3.4 kilograms of the same anhydrous crystal of dexlansoprazole reported in Example 2, with d-spacings at 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41

and 3.11 Angstrom. The optical purity of the final crystal of Reference Example 4 had an optical purity of 100% e.e., compared to the optical purity of 99.8% e.e. for the anhydrous crystal of Example 2. *See id.* at col.10, ll.13-24; *see also id.* at col.11-12, tbl. 2.

v. Experimental Example 1

65. Experimental Example 1, titled "Suppressive action on gastric mucosal injury due to stress of water immersion restraint in rat," TX 0001-0006 to -0007 ('058 Patent) at col.12, l.46 to col.13, l.16, describes the administration of dexlansoprazole to a treatment group of rats. Thirty minutes after the administration of dexlansoprazole, rats in treatment and control groups were subjected to a standard stress test in which they were partially immersed in water in a standing position for 5 hours. Following the stress test, the gastric mucosal injury to each rat's stomach was evaluated to determine the protective value of dexlansoprazole. *See id.*

66. This experiment demonstrated that dexlansoprazole is effective at inhibiting intragastric acid section. *See* TX 0001-0007 ('058 Patent) at Table 4 (showing 98% suppression of gastric mucosal injury in animals that received dexlansoprazole).

b. Amorphous Dexlansoprazole

67. Reference Examples 1 and 2 of the '282 Patent describe two slightly different methods for synthesizing highly pure preparations of the amorphous solid of dexlansoprazole. TX 1055 ('282 Patent) at col.7, l.51 to col.8, l.7 (Reference Example 1); *id.*, col.8, ll.9-29 (Reference Example 2).

68. In Reference Example 1, chiral high pressure liquid chromatography ("HPLC") was used to separate 3.98 grams of racemic lansoprazole into its optically active isomers. *See* TX 1055-0006 ('282 Patent) at col.7, l.51 to col.8, l.7 (Reference Example 1). Racemic lansoprazole was dissolved in the mobile phase (solvent) and acetonitrile before separation by HPLC. *See id.* Fractions of the (R+)-enantiomer were collected from the chromatography column, the individual lots were combined and dissolved in ethanol, and filtered. *See id.*

69. To prevent decomposition of the filtrate that resulted from the chiral column chromatography and filtration process described in Reference Example 1, the Takeda inventors added hexane quickly to the material. *See* Trial Tr. (Atwood Direct) 961:3-14. This solution of hexane and dexlansoprazole was then evaporated to dryness to yield 1.6 grams of solid amorphous

dexlansoprazole, with an e.e. of 97.6%. *See* TX 1055 ('282 Patent) at col.7, l.51 to col.8, l.7 (Reference Example 1).

70. By repeating these steps, the Takeda inventors were able to obtain 1.37 grams of solid amorphous dexlansoprazole with an optical purity greater than 99.9% e.e. TX 1055 ('282 Patent) at col.7, l.51 to col.8, l.7 (Reference Example 1) ("1 shot: 20-25 mg" and reporting the separation of 3.98 grams).

71. In Reference Example 2, Takeda obtained a larger quantity (9.31 grams) of solid amorphous form of dexlansoprazole. In this example, triethylamine, a base, was used instead of hexane to stabilize the material. *Id.*, col.8, ll.9-29 (Reference Example 2); *cf. id.* (Kamiyama Direct) 106:18-108:4; *see also* TX 0722-0002 (SSCI document entitled "Standard Polymorph Screen") ("TAK-390 [dexlansoprazole] degraded in solution over time but was stabilized by addition of triethylamine.").

8. The Patents-in-Suit

72. The four patents-in-suit are all part of the same patent family, with the same inventors and essentially the same specifications. These patents claim priority to a Japanese patent application filed June 17, 1999. *See* TX 0001 ('058 Patent); TX 0002 ('276 Patent); TX 1054 ('971 Patent); TX 1055 ('282 Patent). All claim June 17, 1999 as their earliest priority date.

a. The '058 Patent

73. The '058 Patent issued on October 8, 2002.

74. Claim 1 of the '058 Patent requires "[a] crystal of (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole wherein the x-ray powder diffraction analysis pattern has characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom." TX 0001-0008 ('058 Patent) at col.14, 11. 25-30 (claim 1).

75. The Court construed the disputed term "a crystal of" in claims 1 and 3 of the '058 Patent to mean "regularly repeating pattern of molecules with long range order extending in three dimensions." Similarly, the Court construed the disputed term "a crystalline compound of" in claims 2 and 3 of the '276 Patent and claims 6 and 7 of the '971 Patent to mean "regularly

repeating pattern of molecules with long range order extending in three dimensions." Claim Construction Order [D.N. 106], 3:11-cv-840, at 70.

76. The Court also construed the disputed term "characteristic peaks at interplanar spacings (d)" in claim 1 of the '058 Patent and claim 7 of the '971 Patent to mean "peaks in the x-ray powder diffractogram of a crystal that uniquely identify that crystal, denoted by distances between lattice planes in a crystal as measured by a diffraction experiment and defined by Bragg's law, within normal experimental error of x-ray powder diffraction." *Id.*

77. The two-theta values that correspond to the d-spacings given in claim 1 of the '058 Patent for the anhydrous crystal are: 7.56, 13.06, 15.16, 15.44, 20.04, 21.72, 22.56, 22.82, 24.08. *See* TX 0001-0007 ('058 Patent) at col.11-12, tbl.2.

78. Claim 3 of the '058 Patent depends from claim 1 and requires "[a] pharmaceutical composition which comprises the crystal according to claim 1 and a pharmaceutically acceptable excipient, carrier or diluent." TX 0001-0008 ('058 Patent) at col.14, 11.37-39 (claim 3).

b. The '276 Patent

79. The '276 Patent issued on December 16, 2003. TX0002 at 45.

80. Claim 2 of the '276 Patent requires "[a] crystalline compound of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1 H-benzimidazole." TX 0002-0008 ('276Patent) at col.14, 11.59-61 (claim 2).

81. Claim 3 of the '276 Patent requires "[a] pharmaceutical composition comprising: a crystalline compound of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1 H-benzimidazole or a salt thereof; and a pharmaceutically acceptable excipient, carrier or diluent." TX 0002-0008 ('276 Patent) at col.14, 11.62-67 (claim 3).

c. The '971 Patent

82. The '971 Patent issued on September 6, 2005. TX 1054.

83. Claims 6 and 7 of the '971 Patent depend, directly or indirectly, from claim 5. Claim 5 requires "[a] method of treating reflux esophagitis in a mammal in need thereof which comprises administering to said mammal an effective amount of a crystalline compound of (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole or a salt thereof

and a pharmaceutically acceptable excipient, carrier or diluent." *See* TX 1054 ('971 Patent) at col. 15, ll. 8-13 (claim 5).

84. The Court construed the disputed term "effective amount" in claim 5 of the '971 Patent to mean "an amount sufficient to help ameliorate or cure reflux esophagitis." Claim Construction Order [D.N. 106], 3:11-cv-840, at 71.

85. Takeda and Impax have further agreed that the term "reflux esophagitis" in claim 5 of the '971 Patent means "inflammation or esophageal symptoms caused by gastroesophageal reflux disease (GERD) of the erosive or non-erosive type." Stipulated Facts in Joint Proposed Final Pretrial Order ("Stipulated Facts") [Case No. 3:11-cv-840, D.N. 277] ¶ 9.

86. Claim 6 further specifies that "said crystalline compound is (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole." TX 1054 ('971 Patent) at col. 15, ll. 14-16 (claim 6).

87. Claim 7 also depends from claim 5 and specifies that "said crystalline compound has an x-ray powder diffraction analysis pattern with characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom." *See* TX 1054 ('971 Patent), col. 15, ll. 17-21 (claim 7).

88. The d-spacings listed in claim 7 are the same d-spacings listed in claim 1 of the '058 Patent. *See* TX 0001-008 ('058 Patent) at col.14, 11.25-30 (claim 1).

d. The '282 Patent

89. The '282 Patent issued on June 15, 2010. TX 1055. It is the first patent in this family of patents to claim an amorphous compound of dexlansoprazole (rather than a crystal form), or a "salt thereof." TX1055-0001; TX1055 at 15:3-8; TX0305; Trial Tr. (Kamiyama Cross) 127:9-13. Prior to 1999, Takeda had not made a salt of dexlansoprazole and the specification of the '282 Patent does not include a description of how to make an amorphous salt. Trial Tr. (Kamiyama Cross) 127: 14-17, 130: 8-10.

90. Claim 1 of the '282 Patent requires an "amorphous compound of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole." TX1055 ('282 Patent) at col. 15, ll. 3-8 (claim 1).

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91. The Court has construed the term "amorphous compound" in claims 1 and 2 of the '282 Patent to mean "a non-crystalline solid that lacks the long-range order characteristic of a crystal." Claim Construction Order [D.N. 106], 3:11-cv-840, at 71.

92. Claim 2 of the '282 Patent, which depends from claim 1, requires a "pharmaceutical composition comprising the amorphous compound according to claim 1 and a pharmaceutically acceptable excipient, carrier or diluent." TX 1055-0010 ('282 Patent) at col. 15, ll. 6-8 (claim 2).

C. Facts Regarding Infringement of '276 Patent by Handa

93. As noted above, claim 2 of the '276 Patent requires a crystalline compound of dexlansoprazole; claim 3 of the '276 Patent requires a pharmaceutical composition comprising a crystalline compound of dexlansoprazole and a pharmaceutically acceptable excipient, carrier, or diluent. TX 0002-0008 at col.14, 11.59-67 ('276 Patent) at claims 2 and 3.

94. Handa currently is seeking approval to market a 60-mg dose of dexlansoprazole. *See* Stipulated Facts ¶ 3. This ANDA product is a pharmaceutical composition that contains at least one pharmaceutically acceptable excipient. *See id.* at ¶ 6.

95. Handa uses the amorphous form of dexlansoprazole in the manufacturing process for the ANDA product. Liu Dep. Tr. 55:20-56:5. Takeda contends that a portion of the amorphous solid of dexlansoprazole used to manufacture Handa's ANDA product converts to a crystalline form during the manufacturing process. Handa asserts that while it is possible one of the excipients used in the ANDA product converts to a crystalline form during the manufacturing process, there is no evidence that any of the dexlansoprazole converts to a crystalline form. Although the Court previously found that Handa's drug product contains amorphous dexlansoprazole, it left open the possibility that it may contain both amorphous and crystalline dexlansoprazole.

96. At trial, Takeda's expert Dr. Allan Myerson testified regarding infringement of the '276 Patent.

97. Handa's expert Dr. Robin Rogers testified regarding his opinion that Handa does not infringe the '276 Patent. Portions of the deposition of Dr. Bill Liu, Handa's chief executive officer and president, were played for the Court during trial and Dr. Liu also appeared in person to testify.

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1. Overview of Handa's ANDA Product

98. Handa's ANDA product consists of two types of pellets, Pellet L and Pellet S. TX 390-0008 (ANDA excerpt). The enteric coatings used to coat these two types of pellets are soluble at different pH levels so that they will release the drug at different places in the gastrointestinal ("GI") tract. TX 0390-0008 (Excerpt of Handa ANDA). Otherwise, the L and S Pellets are largely the same. Both are made up of sugar spheres on which the dexlansoprazole drug substance and various excipients are layered to create enteric coated pellets, and the same active-layered spheres are used in both types of pellets. Trial Tr. (Myerson Direct) 189:10-25; *see* TX 390-0010 and -0011 (listing the components of Pellets L and Pellets S). The active-layered spheres are formed by spraying a dispersion, that is, a mixture in which some components are not dissolved, of the active ingredient and various excipients on to the sugar spheres. *See* Trial Tr. (Myerson Direct) 189:3-7, 197: 17-23; *see also* TX 0390-0021 to -0023 (overview of manufacturing process, describing the mixture as a "dispersion").

99. The excipients in the active-layered spheres of Handa's drug product are:

- Sugar spheres, which "basically act as a carrier" or "solid support to spray [the] dispersion on." Trial Tr. (Myerson Direct) 190:14-191:18.
- Calcium hydroxide, which is an inorganic compound used as a stabilizer to maintain a basic pH environment for the active layer. Trial Tr. (Myerson Direct) 191:21-24; TX 0390-0009.
- Hydroxypropylcellulose ("HPC"), a polymer used as a binder, allowing the drug substance and excipients to adhere to the sugar sphere. Trial Tr. (Myerson Direct) 191:25-192:7; TX 0390-0009.
- The right-handed enantiomer of mannitol, known as D-mannitol. Trial Tr. (Myerson Direct) 208:21-210:1. Mannitol is an organic compound that is used as a filler. Trial Tr. (Myerson Direct) 192:8-11; TX 0390-0009.
- Sodium lauryl sulfate, also known as sodium dodecyl sulfate ("SLS" or "SDS"), a surfactant that stabilizes the drug coating dispersion during drug layering. Trial Tr. (Myerson Direct) 192:12-17; TX 0390-0009.

100. Acetone and water also are used as solvents in Handa's manufacturing process for the active-layered spheres. *See* Trial Tr. (Myerson Direct) 192:18-193:1.

101. The manufacturing process for the active-layered spheres of Handa's drug product is set forth in detail in the manufacturing batch record for the active-layered spheres of the exhibit batch submitted by Handa to the FDA, Batch No. 1000540. *See* TX 1010 (Manufacturing Batch Record); Trial Tr. (Myerson Direct) 195:4-25; *see* Liu Dep. Tr. 68:25-71:14 (describing manufacturing process); Trial Tr. (Liu Cross) 314:13-16 (admitting that the manufacturing process for Batch No. 1000540 was the same manufacturing process as for Handa's final ANDA product); *id.* (Rogers Cross) 446:10-447:1.

102. First, 35.0 kilograms of acetone and 0.395 kilograms of purified water were combined. *See* TX 1010-0003; Trial Tr. (Myerson Direct) 196:8-16. Next, calcium hydroxide was added to the acetone/water mixture. *See* TX 1010-0003. Calcium hydroxide is "pretty insoluble" in acetone and water, so adding the calcium hydroxide would have created a dispersion. *See* Trial Tr. (Myerson Cross) 249:9-250:17; *id.* (Myerson Direct) 196:17-23. Next, amorphous solid dexlansoprazole was dissolved into this mixture. *See* TX 1010-0004; Trial Tr. (Myerson Direct) 196:24-197:1. A small amount of SLS (0.547 kilograms) was then added to this mixture. *See id.* Next mannitol was added. Because mannitol is practically insoluble in acetone, and a relatively large amount of mannitol was added (8.225 kilograms), most if not all of the mannitol would not be dissolved. *See* Trial Tr. (Myerson Direct) 197:4-12; *id.* (Rogers Cross) 454:18-20; TX 1010-0005.

103. In a separate container, 3.080 kilograms of HPC was added to another 31.0 kilograms of acetone. *See* Trial Tr. (Myerson Direct) 197:13-17; TX 1010-0005. This HPC/acetone mixture was then combined with the acetone-water mixture containing calcium hydroxide, dexlansoprazole, SLS, and mannitol. *See* Trial Tr. (Myerson Direct) 197:14-21; TX 1010-0005. At this point, 16 kilograms of acetone and 0.395 kilograms of water were present in the dispersion. *See* Trial Tr. (Myerson Direct) 198: 1-2. The final dispersion was sprayed onto sugar spheres and the product was dried at 70 degrees Celsius for one hour, thereby removing the acetone and water. *See* Trial Tr. (Myerson Direct) 198:3-9; TX 1010-0007.

2. XRPD Analysis of the Active-Layered Spheres of Handa's ANDA Product

104. Following the manufacture of Batch No. 1000540, Handa tried to determine whether the amorphous dexlansoprazole may have converted to a crystalline form during the manufacturing process. *See* Trial Tr. (Myerson Direct) 198:10-199:2; Trial Tr. (Rogers Cross) 447:2-10; *see* TX 1032A (Handa Sample Request Form).

105. Handa labeled a sample of the active-layered spheres from its exhibit batch (Batch No. 1000540) as sample "E64" and sent it to Zhejiang University for XRPD analysis. *See* Trial Tr. (Myerson Direct) 199:12-200:2; *id.* (Liu Direct) 292:15-20 (admitting that E64 corresponds to the exhibit batch for Handa's ANDA product); *see also* TX 1032A-0023 (describing analysis of sample E64, also referred to as the "Fourteenth sample submission"). Mr. Lui testified that this was the only exhibit batch and the one Handa relied on when it submitted its ANDA to the FDA. Trial Tr. (Liu Cross) 314:13-315:14.

106. Trial Exhibit 1032A is the English translation of the sample request form generated by Hangzhou Handa. Hangzhou Handa is a wholly-owned subsidiary of Handa and participated in the development of Handa's ANDA product. *See* Liu Dep. Tr. 175:7-16 (describing sample request form); *id.* 40:23-41:4 (describing relationship between Hangzhou Handa and Defendant Handa). The sample request form for E64 lists the same excipients used in Handa's manufacturing process, namely, HPC (code name F4), sucrose sphere (code name F5), calcium hydroxide (code name F8), mannitol (code name F17), and SLS (code name F19). *See* TX 1032A-0001, -0007, -0013, and -0019 (Hangzhou Handa's sample request form) (providing code names for excipients); *see also* Trial Tr. (Myerson Direct) 199:3-11.

107. According to Handa's sample request form, the purpose of the XRPD analysis of Batch No. 1000540 was to "[d]etermine whether the raw material drugs in the samples are amorphous or crystalline." TX 1032A-0023; Trial Tr. (Liu Cross) 317:12-16; Liu Dep. Tr. 181:9-14 (agreeing that it would be "fair to say that their objective was to characterize the drug substance in the sample"); Trial Tr. (Rogers Cross) 447:2-10 (agreeing that the purpose of this experiment was to determine whether the dexlansoprazole in the active-layered spheres was amorphous or crystalline). Dr. Liu, who testified that he designed the XRPD experiments, also testified at trial

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that Handa performed the XRPD analysis of Batch No. 1000540 to find out whether or not the Handa product would infringe any Takeda patents, including the '276 Patent. Trial Tr. (Liu Cross) 326:5-10.

108. At Handa's request, Zhejiang University also did XRPD analyses of the raw excipients used in the manufacture of Handa's active-layered spheres. *See* Trial Tr. (Myerson Direct) 206:9-210:1; Liu Dep. Tr. 175:3-10. Dr. Myerson confirmed that the x-ray patterns reported in Trial Exhibit 0034 for the raw excipients correspond to the known crystal patterns for those excipients. *See* Trial Tr. (Myerson Direct) 210:3-9. These x-ray patterns demonstrate that the sugar spheres, SLS, calcium hydroxide, and mannitol are crystalline. Trial Tr. (Myerson Direct) 247:3-11; *see also* TX 0034-0005 (XRPD for sugar spheres); TX 0034-0013 (XRPD for calcium hydroxide); TX 0034-0029 (XRPD for mannitol); TX0034-0033 (XRPD for SLS). HPC is a mixture of crystalline and amorphous regions, and its XRPD lacks sharp peaks. *See id.* (Myerson Direct) 208:6-16; *id.* (Myerson Direct) 247:3-11; TX 0034-0004 (XRPD for HPC).

109. After performing the XRPD analysis on the active-layered spheres of Handa's drug product, Handa compared the crystal peaks in the x-ray patterns for these raw excipients against the x-ray pattern for the active-layered spheres in its ANDA product, Batch No. 1000540. *See* Trial Tr. (Myerson Direct) 205:19-206:8; *id.* (Rogers Cross) 449:2-10. This comparison or "subtraction" of the peaks revealed that most of the peaks in the x-ray pattern for the active-layered spheres in Handa's drug product correspond to excipients. Compare TX 1035-0002 (XRPD of sample E64) with TX 0034-0005 (XRPD for sugar spheres); TX 0034-0013 (XRPD for calcium hydroxide); TX 0034-0029 (XRPD for mannitol); TX 0034-0033 (XRPD for SLS); *id.* (Myerson Direct) 205:19-206:8; *id.* (Myerson Direct) 210:10-212:22. However, two peaks, at 6.4 and 10.0 degrees two-theta, did not correspond to any known polymorphs of the excipients. *See* Trial Tr. (Myerson Direct) 212:20-213:7; *see also* Trial Tr. (Liu Direct) 296:3-6 (testifying that "those two [peaks] do[] not come from those single pure excipients"); *id.* (Rogers Cross) 451:3-16 (admitting that there are no peaks in the raw excipients that match the peaks at 6.4 and 10.0).

110. Dr. Lui testified that he did not know whether the diffraction peaks at 6.4 and 10.00 were attributable to the drug substance or the excipients. This testimony was not credible. Handa's

own contemporaneous documents show that Handa concluded, based on the XRPD analysis conducted at Zhejiang University, that its ANDA product contained crystalline dexlansoprazole. In particular, the results for the XPRD analysis for Batch No. 1000540 were described as follows: "Samples are crystalline and the characteristic diffraction peaks are 6.4, 10.0 (2theta)." TX 1032A-0023. Further, the stated goal of this analysis was to "[d]etermine whether the raw material drugs in the samples are amorphous or crystalline." TX 32A -0023. In addition, Dr. Liu admitted that, even though this result was originally reported by Zhejiang University, it was incorporated into the Handa sample request form at Trial Exhibit 1032 (and TX 1032A) by an employee of Hangzhou Handa. *See* Liu Dep. Tr. 175:12-16; Trial Tr. (Liu Redirect) 341:10-12. Also, Enjun Fu, a formulation scientist at Hangzhou Handa, described the results of the XRPD analysis on the active-layered spheres from the exhibit batch to Handa's Zack Shen, the general manager of Hangzhou Handa. *See* TX 1035 (4/8/2010 email with XRPD chart) & TX 1035A (English translation of email only); Trial Tr. (Liu Cross) 323:3-24. The cover email from Mr. Fu uses the same language as that on the sample request form: "The samples are crystalline and their characteristic diffraction peaks are 6.4, 10.0 (2 theta)." TX 1035A-0001; Trial Tr. (Liu Cross) 323:3-24. It is significant that the diffractogram for the active-layered spheres shows approximately fifty XRPD peaks, yet Handa described only the peaks at 6.4 and 10.0 degrees two-theta as "characteristic," indicating these peaks characterized a crystal form of dexlansoprazole. *See* TX 1035-0002 (XRPD of sample E64); TX 1035A-0001 (Mr. Fu's email).

111. Dr. Myerson testified persuasively that the only purpose for performing XRPD analyses on the pure excipients used in Handa's manufacturing process would be to eliminate them as the source for the crystal peaks at 6.4 and 10.0 degrees in Handa's drug product. *See* Trial Tr. (Myerson Direct) 201:24-202:12.

3. Solvias Testing of Handa's Finished ANDA Product

112. Takeda retained a laboratory, Solvias AG, to test Handa's ANDA product, and Solvias confirmed that that product exhibits crystal peaks at 6.4 and 10.0 degrees two-theta. *See* TX 0129-0014 (Solvias Report) ("Patent application WO2011/063150 of HANDA Pharmaceuticals mentions two characteristic peaks at 6.4 and 10.0° in 2θ. Both peaks were found to be present in

the PXRD pattern of both dosage forms (samples PP443-K9 and PP443-K10).").

113. Solvias also confirmed that the peaks at 6.4 and 10.0 degrees two-theta cannot be attributed to mannitol or the sugar spheres. *See* TX 0129-0015, fig. 5.2 (XRPD patterns of the granules in Handa's capsule, mannitol, and sucrose); Trial Tr. (Rogers Direct) 435:19-438:1.

4. Whether the Crystal Peaks at 6.4 and 10.0 Can Be Attributed to Any Excipient in Handa's ANDA Product

114. Handa admits that the peaks at 6.4 and 10.0 degrees two-theta are in its finished ANDA product and that they cannot be attributed to any of the raw excipients used in the manufacture of the active-layered spheres of Handa's drug product. Trial Tr. (Rogers Direct) 422:23-423:6 ("[T]hey're reporting that they had those two peaks that were not attributable to the excipients in their original form, before processing."); Trial Tr. (Liu Direct) 296:3-6 (testifying that "those two [peaks] do[] not come from those single pure excipients"). In addition, Dr. Liu testified that he does not know the source of the peaks at 6.4 and 10.0. Trial Tr. (Liu Cross) 327:3-18; 338:22-339:11.

115. Nonetheless, Handa contends the peaks at 6.4 and 10.0 degrees two-theta are attributable to polymorphs of the excipients. However, Dr. Rogers admitted that he did not know the details of the science behind the manufacturing process well enough to be able to say whether or not any of the excipients converted to any other polymorph during the manufacturing process that might explain the two peaks. Trial Tr. (Rogers Cross) 456:25-457:22; 458:25-459:13.

116. The preponderance of the evidence showed that the peaks at 6.4 and 10.0 cannot be attributed to any of the excipients, and that they are attributable to a crystalline form of dexlansoprazole in Handa's drug product.

a. SDS and Sugar Spheres

117. Two of the excipients in Handa's active-layered spheres – SDS and the sucrose spheres – cannot be the source of the crystalline peaks in Handa's ANDA product, because Handa obtained these same peaks using a formulation that did not include these excipients. *See* TX 1031 (WO 2011/063150) ("the '150 patent application"). Example 1 of the '150 patent application , filed by Handa, describes a method for combining dexlansoprazole with the excipients calcium hydroxide,

mannitol, and HPC in acetone, applying this dispersion to a glass plate, and then drying the mixture. *See* TX 1031-0030 to -0031 (Example 1); Trial Tr. (Myerson Direct) 214:23-215:16. Dr. Liu testified that the formulation method set forth in Example 1 was only "slightly different" from the manufacturing process used for Handa's active-layered spheres. *See* Liu Dep. Tr. 169:18-170:2 (noting that the only difference was that in Handa's manufacturing process the HPC is dissolved separately in acetone then added to the dispersion with the other excipients); Trial Tr. (Liu Cross) 337:5-338:4. Dr. Myerson also noted that the experiment in Example 1 did not include water as in the manufacturing process. However, Example 1 used the sesquihydrate form of dexlansoprazole, which would have contributed the same ratio of water that was used to make the active-layered spheres of the exhibit batch. *See* Trial Tr. (Myerson Direct) 215:17-216:10.

118. Despite the fact that Handa did not use SDS or sugar spheres in this experiment, the resulting solid exhibited crystal peaks at 6.4 and 10.0 degrees two-theta. *See* TX 1031-0031. As a result, and as Dr. Rogers admitted at trial, the peaks at 6.4 and 10.0 degrees two-theta cannot be attributed to SDS or the sucrose spheres. *See* Trial Tr. (Myerson Direct) 217:13-21; *id.* (Rogers Cross) 461:8-11 ("I do think that's reasonable").

119. Dr. Myerson also observed that, while the '150 application reports only seven crystal peaks for the formulation described in Example 1, many more peaks must have been present because of the presence of calcium hydroxide and mannitol in the formulation. See Trial Tr. (Myerson Direct) 217:22-218:12. Thus, Handa must have once again compared the peaks in its formulation to the known peaks for the raw excipients and concluded that the remaining peaks would be associated with crystalline dexlansoprazole. This conclusion is corroborated by the following admonition in the '150 application:

> The x-ray diffraction patterns of formulations containing inactive ingredients, (i.e. excipients) requires careful analysis. The presence of peaks relating to the inactive ingredients can be obscuring and an identification of the peaks relating to the inactive ingredients can be helpful in analysis of the pattern. For analysis of the formulations containing inactive ingredients a set of x-ray diffraction pattern for certain inactive ingredients were obtained.

TX 1031-0020 ('150 application) at [0055]; *see also* Trial Tr. (Myerson Direct) 218:16-219:4 ("I think [this] paragraph implies that they took into account the peak[s] of the excipients when doing

their analysis").

b. Mannitol

120. The only polymorph of any excipient that Dr. Rogers identified as a potential source of the novel crystal peaks in Handa's drug product was delta mannitol. *See* Trial Tr. (Rogers Cross) 452:11-25.

121. There are several known polymorphs of mannitol. *See* Trial Tr. (Myerson Direct) 222:5-9; *id.* (Rogers Direct) 425:9-10. Delta D-mannitol is a polymorph of D-mannitol. *Id.* (Myerson Direct) 209:9-210:1. Delta D-mannitol has a peak at about 10.0 degrees two-theta. *Id.* (Rogers Direct) 425:14- 26:1. Beta D-mannitol, another polymorph of D-mannitol, does not have a peak at 10.0 degrees two-theta. *Id.* (Myerson Direct) 208:7 - 209:13. Handa uses beta D-mannitol in its manufacturing process. *See id.*

122. Further, Dr. Rogers admitted that delta D-mannitol could not be the source of the peak at 6.4 degrees two-theta and that he could provide no explanation for the peak at 6.4. *See* Trial Tr. (Rogers Cross) 452:25-453:6 (admitting that he said at his deposition that he has "no explanation for the distinctive peak at 6.4"). Dr. Rogers also admitted that he is not offering an opinion that delta D-mannitol is present in Handa's formulated product and that he had made no such determination. *See* Trial Tr. (Rogers Cross) 454:4-25.

123. Accordingly, the Court finds that the mannitol in Handa's ANDA product is not the source of the peak at 6.4 degrees two-theta and is unlikely to be the source of the peak at 10.0 degrees two-theta.

c. Other Excipients

124. Dr. Myerson testified that, with the exception of mannitol, discussed above, no known polymorphs of any other excipient used by Handa have crystal peaks at 6.4 and 10.0 degrees two-theta. *See* Trial Tr. (Myerson Direct) 225:24-226:2. Dr. Rogers also testified that he could not explain how any of the excipients other than mannitol might change to another polymorphic form during the manufacturing process. *Id.* (Rogers Cross) 458:21-459:20.

125. Because calcium hydroxide is an inorganic molecule, polymorphs of calcium hydroxide will not have "low-angle peaks" like those at 6.4 and 10.0 degrees two-theta. *See* Trial Tr.

(Myerson Direct) 207:20-208:5; *id.* 226:3-8 (adding that "I'm not aware of calcium hydroxide polymorphs"). In addition, there is no evidence that calcium hydroxide can form polymorphs such as hydrates or acetone solvates with the acetone and water present during Handa's manufacturing process. *See* Trial Tr. (Myerson Direct) 227:22-24. Because calcium hydroxide is "pretty insoluble" in both acetone and water, it would be unlikely to form a new polymorph in the acetone-water dispersion. *See id.* (Myerson Cross) 249:9-250:17; *id.* (Myerson Cross); *see also* 244:14-22 (testifying that if one of Handa's excipients does not dissolve then it will not change polymorphic form).

126. A polymorph of HPC, which is only semi-crystalline, would not demonstrate and could not explain strong, sharp peaks at 6.4 and 10.0 degrees two-theta. *See* Trial Tr. (Myerson Direct) 226:9-10.

127. Dr. Myerson also testified that there is no mechanism by which a co-crystal, meaning a crystal composed of two molecules that combine to form a new molecule, could form from the excipients in Handa's formulation. *See* Trial Tr. (Myerson Direct) 228:15-229:13; *id.* (Myerson Cross) 252:6-253:4 (testifying that in order for an excipient to form a new crystalline complex, it would need to be dissolved, but "the only things that are dissolved in that solution are HPC . . . , SDS, and very small amounts of calcium hydroxide [and] very small amounts of mannitol," so not enough of any excipient is dissolved in water to form a crystalline complex). Furthermore, as discussed above, the fact that the crystal peaks at 6.4 and 10.0 degrees are present in the formulation in Example 1 of the '150 application, *see* TX 1031-0031, means that a complex with SDS or the sugar spheres cannot be responsible for the peaks at 6.4 and 10.0 degrees.

128. Accordingly, the Court finds that calcium hydroxide, HPC, and/or mannitol are not the source of the peaks at 6.4 or 10.0 degrees two-theta.

5. Statements in Handa Documents Relating to Whether Dexlansoprazole in its Drug Product Crystallizes During the Manufacturing Process

129. Other Handa documents acknowledge that amorphous solid dexlansoprazole can crystallize when it is placed in solution.

130. For example, an experimental plan drawn up by Handa states that "[s]table anhydrous

crystalline dexlansoprazole can be produced by recrystallization from amorphous dexlansoprazole dissolved in acetone." TX 1030A-0001; *see also* Liu Dep. Tr. 163:12-24; *id.* 165:18-21; 166:2-4. Dr. Liu testified at his deposition that amorphous dexlansoprazole "could result" in a crystal when it is dissolved in acetone. *See* Liu Dep. Tr. 165:13-17. "The amorphous dexlansoprazole, after dissolving in acetone, when you evaporate the acetone, it will become some type of crystals. It may not be entirely A, the anhydrous dexlansoprazole. It could be some of the other — the other forms. So that's what we find." Liu Dep. Tr. 166:6-24 (adding that Handa did not attempt to characterize that crystal); *see also* Trial Tr. (Myerson Direct) 230:12-16 (testifying that the fact that amorphous dexlansoprazole can crystallize from acetone supports his opinion that the peaks at 6.4 and 10.0 are attributable to the drug substance).

131. Similarly, a Handa development document states: "When we dissolve amorphous dexlansoprazole to acetone, disperse inactive ingredients to acetone, and coat them on the sucrose spheres, the product is stabilized based on the Table 6 too. The reason is that amorphous dexlansoprazole is transformed into crystal form when it is dissolved in acetone and sprayed onto the sucrose spheres." TX 1028A-0007 to -0008 (spreadsheet). Dr. Myerson testified that, even though the formulation described in this document did not contain water, the amount of water in Handa's manufacturing process is so small that the absence of water would not change the fact that a crystal is formed. *See* Trial Tr. (Myerson Direct) 231:1-16.

132. Accordingly, Trial Exhibits 1030A and 1028A support the conclusion that during Handa's manufacturing process amorphous dexlansoprazole can convert to a crystalline form of dexlansoprazole. *Id.*

133. In addition, Handa produced a spreadsheet that compares crystallinity data identified for Handa's drug product with crystallinity data reported in two Takeda patents: U.S. Patent No. 6,462,058, which issued from the parent application for the '276 Patent, and EP1552833, a European patent that describes a hemihydrate crystal of dexlansoprazole. *See* TX 1036A-0001. The top 15 rows list the two-theta angles, d-spacings, and relative intensities from XRPD analysis provided in the '276 Patent at Tables 2 and 3 for the anhydrate and sesquihydrate crystals of dexlansoprazole, respectively. *Id.*; Trial Tr. (Myerson Direct) 219:5-221:12. Cell A29 states, "Our

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Polymorph," and then lists four diffractogram peaks, including the peaks at 6.4 and 10.0 degrees two-theta described above. *Id.*

134. As discussed above, the term "polymorph" generally refers to crystalline forms of a compound, particularly when used in conjunction with x-ray diffraction data. *Id.* This document further evidences Handa's own belief that the dexlansoprazole drug substance in Handa's ANDA product is crystalline, although with a different structure than the crystals specifically characterized in the '276 Patent. *See* Trial Tr. (Myerson Direct) 221:5-12 ("[I]t appears that whoever was the author of this document thought that they had a new crystalline polymorph of dexlansoprazole.").

6. Failure of SSCI's Standard Polymorph Screen to Identify a Polymorph of Dexlansoprazole With Characteristic Peaks at 6.4 and 10.0

135. To support its contention that the drug substance in the active-layered spheres of Handa's ANDA product cannot be the source of the peaks at 6.4 and 10.0 degrees two-theta, Handa points to the fact that SSCI, a contract laboratory retained by Takeda in connection with its New Drug Application for Dexilant, did not identify a crystalline form with those peaks.

136. In 2009, SSCI completed a "Standard Polymorph Screen" on dexlansoprazole, using the anhydrous crystal of dexlansoprazole disclosed in the '276 Patent, referred to as "Form A," as a starting point. Gushurst Dep. Tr.11 122:07-123:12. SSCI characterized several polymorphs of dexlansoprazole, including several hydrates. *See, e.g.,* TX 0722-0002 (Standard Polymorph Screen).

137. The Standard Polymorph Screen conducted by SSCI was not intended to be exhaustive, however. SSCI offers at least two types of polymorph screens: a standard screen that "is designed to identify most of the solid forms of [a] drug substance," and a Super Screen, a more extensive and expensive screen, that is intended to be comprehensive. *See* Trial Tr. (Rogers Cross) 465:11-466:9; *id.* (Myerson Direct) 238:5-11. For dexlansoprazole, SSCI conducted only its standard screen. *Id.* (Rogers Cross) 465:11-466:9.

138. No polymorph screen can identify with certainty every possible polymorph. Trial Tr. (Myerson Direct) 238:12-20 ("Those of us who are in this business know you can do an infinite

number of experiments, and somebody might find a new polymorph of something 20 years after a drug has been discovered or a molecule has been around."); *see id.* (Myerson Direct) 184:22-185:1. In fact, SSCI failed to identify at least one other known form of dexlansoprazole called Form X in its screen. *See* TX 0366-0002 (SSCI, Characterization Studies of Form X and Form A of TAK-390 (Apr. 14, 2009)) ("A new TAK-390 form, form X has been discovered by Takeda."). Takeda itself generated Form X by heating various different hydrated polymorphs of dexlansoprazole, as well as amorphous dexlansoprazole. *See* TX 69x45-0005 (Manufacturing Method and Analytical Data of Form X (TAP/Takeda CMC meeting in Osaka, March 12-13, 2008)); *see also* Trial Tr. (Rogers Direct) 433:13-19 (stating that Form X "was not obtained by crystallization from solution," but rather was a "transformation of an amorphous form or of a hydrated dexlansoprazole") (emphasis added). SSCI later determined that Form X is an anhydrous crystal containing amorphous component. *See* TX 366-0008 to -0009; TX 69x45-0003.

139. New polymorphs of drug substances may be discovered at any time. Trial Tr. (Myerson Direct) 184:22-185:1 ("All you can say is that you have found a certain number of polymorphs, but you never know if there's another one that exists"). Nonetheless, dexlansoprazole was first crystallized fairly recently, in 1999. *See* Trial Tr. (Kamiyama Direct) 85:3-5. Form X was discovered just five years ago, in 2008. *See* Trial Tr. (Myerson Direct) 186:20-187:12. In contrast, the excipients in Handa's drug product have been studied for a long time. *See* Trial Tr. (Rogers Cross) 467:14-468:1 ("I think most of them have been studied for a long time."). Therefore, the Court finds that the peaks at 6.4 and 10.0 are attributable to a form of dexlansoprazole.

7. Whether the Peaks at 6.4 and 10.0 are More Likely than Not Attributable to Crystalline Dexlansoprazole

140. For the reasons stated above, the Court finds that the crystal peaks at 6.4 and 10.0 degrees two-theta in the active-layered spheres of Handa's ANDA product are attributable to crystalline dexlansoprazole in Handa's ANDA product.

D. Findings of Fact Related to the Validity of the Crystal-Form Patents ('058, '276 and '971 Patents

141. Impax contends the prior art renders obvious claims 1 and 3 of the '058 Patent and claims

6 and 7 of the '971 Patent.

142. Handa and Impax together contend that the prior art renders obvious claims 2 and 3 of the '276 Patent.

143. At trial, Defendants' expert Dr. Wayne Genck testified regarding his opinion that the asserted claims of the Crystal-Form Patents are invalid.

144. Takeda's expert Dr. Jerry Atwood testified regarding the validity of the asserted claims of the Crystal-Form Patents.

1. The Level of Ordinary Skill in the Art of the Crystal-Form Patents

145. The parties' experts agreed as to the level of skill in the art of the Crystal-Form Patents. These patents focus on organic chemistry, crystallization, and crystal forms. *See* Trial Tr. (Atwood Direct) 901:23-902:13. The level of skill in the art of the invention of the Crystal-Form Patents is either a Ph.D. in chemical engineering or related disciplines or a bachelor's degree in chemistry, chemical engineering, or a related field and three to five years of experience in crystallization and characterization of crystals by routine methods such as x-ray diffraction analysis. *See* Trial Tr. (Atwood direct) 942: 14-18; (Genck direct) 713: 14 - 714: 5.

2. Whether Claims 1 and 3 of the'058 Patent are Obvious

a. Overview of the Prior Art

146. Impax divides the prior art that is the basis for its obviousness challenge into two broad categories. The first category discloses dexlansoprazole, either obtained via asymmetric synthesis (as in Larsson and Von Unge), or separated from racemic lansoprazole via HPLC (as in Katsuki, Tanaka and Borner). The second category of references includes textbooks and manuals that teach general methods of achieving crystallization, including Tietze, Vogel, and Gordon, and also references disclosing methods for crystallizing structurally similar proton pump inhibitors ("PPIs"), including Kato, Nohara, Kohl, and Bohlin. Trial Tr. (Genck Direct) 733: 2-734: 25, 735:22-736:20, 737:12-738:4, 836:11-24.

147. Impax contends claims 1 and 3 of the'058 Patent are obvious based on Larsson, Von Unge and Barberich in view of Kato, Nohara, Kohl, Bohlin, Tietze, Vogel, and Gordon. It also asserts claims 1 and 3 are obvious based on Katsuki, Tanaka, Borner and Erlandsson in view of Kato,

Nohara, Kohl, Bohlin, Tietze, Vogel and Gordon.

148. "Larsson" refers to PCT Publication WO 96/02535 ("Larsson I") (TX 0070) and U.S. Patent No. 5,948,789 ("Larsson II") (TX 0301)). The disclosures of Larsson I and Larsson II are materially the same.

149. "Von Unge" refers to PCT Publication WO 97/02261 ("Von Unge I") (TX 0071)) and U.S. Patent No. 5,929,244 ("Von Unge II") (TX 302)). The disclosures of Von Unge I and Von Unge II are materially the same.

150. "Barberich II" refers to U.S. Patent Application Publication No. 2003/0008903 (TX 0078).[3] The Barberich II reference claims priority to a provisional application filed January 30, 1998. *See* TX 0078-0001.

151. "Kato" refers to PCT Publication WO 98/21201 ("Kato I") and U.S. Patent No. 6,002,011 ("Kato II"). *See* TX 87 (Kato I); TX 69x32 (Kato II). There is no material difference between the disclosures of Kato I and Kato II.

152. "Katsuki" refers to Hisakaza Katsuki et al., "Determination of R(+)-and S(-)- Lansoprazole Using Chiral Stationary-Phase Liquid Chromatography and Their Enantioselective Pharmacokinetics in Humans," Pharm. Res. 13(4):611-15, published in 1996 (TX0073).

153. "Tanaka" refers to Makoto Tanaka, *et al.* "Direct HPLC Separation of Enantiomers of Pantoprazole and Other Benzimidazole Sulfoxides Using Cellulose-Based Chiral Stationary Phases in Reversed-Phase Mode," Chirality 7:612-15 (1995), published in 1995 (TX0069x48).

154. "Borner" refers to K. Borner et al., "Separation of Lansoprazole Enantiomers in Human Serum by HPLC," 47 Chromotgraphia 171 (1998), published in February, 1998 (TX0075).

155. "Nohara" refers to U.S. Patent 4,628,098 (TX 0097), also assigned to Takeda.

156. "Kohl" refers to German Patent Application Publication No. DE 403545 (TX 0086).

157. "Bohlin" refers to PCT Publication WO 98/28294 (TX 0076).

158. "Tietze" refers to Lutz-Friedjan Tietze and Theophil Eicher, *Reactions and Synthesis in the Organic Chemistry Laboratory*, 24-25 (1989) (TX 0080).

[3] Takeda does not concede that Barberich II is prior art to the '058 Patent.

159. “Vogel” refers to Arthur Israel Vogel, *Vogel’s Textbook of Practical Organic Chemistry*, 135-43 (5th ed. 1989) (TX 0081).

160. “Gordon” refers to Arnold Gordon & Richard Ford, The Chemist’s Companion - A Handbook of Practical Data, Techniques, and References, 442-43 (1972) (TX 0082).

161. Larsson I, Von Unge I, and Kato I were before the patent examiner during prosecution and appear on the face of the ’058 Patent. See TX 0001 (’058 Patent), at TX0001-0001.

b. Prior Art Cited by Impax for the Disclosure of Dexlansoprazole

vi. Larsson, Von Unge and Barberich

a. Larsson

162. The goal of the Larsson inventors was to synthesize enantiomers of omeprazole and structurally related compounds for use in pharmaceutical products. *See* TX 0301 (Larsson II) at TX 0301-0002, col.1, ll.53-55.

163. The Larsson inventors state that “[t]he best mode to carry out the present invention known at present is as described in Example 11.” *Id.* at TX 0301-0012, col.21, ll.66-67. Example 11 describes the asymmetric oxidation of omeprazole to form (R+)-omeprazole, followed by the preparation of a sodium salt of (R+)-omeprazole and subsequent crystallization. This process resulted in a crystal of (R+)-omeprazole sodium with an optical purity of 99.6% e.e. *Id.* at TX 0301-0008, col.13, l.52 to col.13, l.14 (Example 11); *see also* TX 0301-0006, col.10, ll.28-33 (indicating that some of the crude products of the asymmetric oxidation reactions Larsson discloses can be crystallized). Accordingly, the preferred embodiment of the Larsson invention involves crystallization. This is consistent with the testimony at trial that crystal forms of compounds were preferred for use in pharmaceutical compositions such as those contemplated in Larsson. *See, e.g.,* Trial Tr. (Genck Direct) 773:5-15.

164. The Larsson inventors describe the synthesis of enantiomers of omeprazole and several structurally related compounds using asymmetric oxidation: Compound (Ia) corresponds to omeprazole; Compound (Ib) corresponds to 5-fluoro-2-[[(4-cydopropylmethoxy-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole; Compound (Ic) corresponds to 5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole;

Compound (Id) corresponds to lansoprazole; Compound (Ie) corresponds to 5-difluoromethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole; Compound (If) corresponds to pariprazole; Compound (Ig) corresponds to leminoprazole; Compound (Ih) corresponds to 2-[(4-methoxy-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)sulphinyl]-1H-benzimidazole. *See* TX 0001 (Larsson II) at TX 0301-0004 to -0005, col.6, l.45 to col.7, l.58.

165. Larsson also discloses the crystallization of several of these compounds and their salts. For example, Larsson was able to crystallize enantiomers of omeprazole and compounds (Ib), (Ic), and (Ie). *See, e.g., id.* at -0007 to -0011. Examples 4 and 9 ((S-)-omeprazole sodium); Examples 10 and 11 ((R+)-omeprazole sodium); Examples 12 and 15 (compound (+)-(Ib)); Examples 13 and 16 (compound (-)-(Ib)); Examples 18 and 19 (compound (-)-(Ic)); Example 20 (compound (+)-(Ic)); Example 23 (compound (-)-(Ie); and Example 24 (compound (+)-(Ie)).

166. Larsson also reports isolating compounds (Ib), (Ic), and (Ih) as solids (not necessarily crystals). *See id.* at Example 14 (compound (-)-(Ib)); Example 17 (compound (+)-(Ic)); Example 29 (compounds (-)-(Ih) and (+)-(Ih)).

167. On the other hand, the Larsson inventors isolated certain sulfoxide compounds only as oils. The sulfoxide compounds that were isolated only as oils include lansoprazole, pariprazole, and leminoprazole. *See id.* at Example 21 ((S-)-lansoprazole); Example 22 ((R+)-lansoprazole); Example 25 ((S-)-pariprazole); Example 26 ((R+)-pariprazole); Example 27 ((S-)-leminoprazole); and Example 28 ((R+)-leminoprazole).

168. Example 22 describes the synthesis and purification of dexlansoprazole, which resulted in an oil. *See* TX 0301-0010 at col.18, ll.5-35 (Example 22); *see also* Trial. Tr. (Rogers Cross) 612:20-23; *id.* (Genck Direct) 735:1-5; *id.* (Atwood Direct) 906:18-21. 182. The first step in Example 22 of Larsson is the asymmetric oxidation of a lansoprazole sulfide (2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]-methyl]thio]-1H-benzimidazole). *See* TX 0301 (Larsson II) at TX 0301-0010, col.18, ll.10-26.

169. The synthesis method described in Example 22 of Larsson consists of the following steps: First, 2.1 grams of lansoprazole sulfide were dissolved in 50 ml of toluene, an organic solvent. *See id.* ll.10-12. To this solution was added (i) water, (+)-diethyl L-tartarate, and titanium (IV)

isopropoxide; this mixture was stirred for 60 minutes at 50° C and then cooled to room temperature. *See id.* ll. 12-16. Next, (ii) N,N-diisopropylethylamine and cumene hydroperoxide were added. *See id.* ll. 16-18. The purpose of steps (i) and (ii) is to oxidize the sulfide to form a sulfoxide, either lansoprazole or more preferably dexlansoprazole. Trial Tr. (Atwood direct) 915: 24 -916:2.

170. This reaction was stirred for 16 hours at room temperature, and then toluene was added to the solution. *See* TX 0301 (Larsson II) at TX 0301-0010, col.18, ll.19-22. Next, the solution was extracted three times with an aqueous ammonia solution. *See id.* ll.22-24. Here, the compound of interest (lansoprazole or its enantiomers) was extracted into the aqueous ammonia solution, leaving behind the organic solvent (including toluene). *Cf. id.* ll. 22-26. The combined aqueous layers were then neutralized by the addition of concentrated acetic ac*id. Id.* ll.24-26.

171. Next, the "workup procedure" employed extraction, evaporation, and flash chromatography. *Id.* ll.26-27. These steps are taken to isolate the compound of interest. The first of these three steps is extraction. The compound of interest would have been extracted into (i.e., separated from the remaining material and dissolved in) the solvent used here, although the solvent that Larsson used is not specified. *See id.*; Trial Tr. (Rogers Cross) at 651:13-20; *id.* (Elder Cross) 394:20-24. The second step is flash chromatography, which is a type of column chromatography. *Cf.* Trial Tr. (Atwood Direct) at 915:23-916:8. The solvent system for the flash chromatography used by Larsson is not disclosed in Example 22. TX 301 (Larsson II) at TX 0301-0010, col.18, ll.26-27; Trial Tr. (Elder Cross) 394:20-24, 395:3-13; *see also id.* (Rogers Cross) 651:13-20 (indicating that Larsson did not specify a solvent for the purification step). These steps resulted in 0.85 grams of a "residue" of dexlansoprazole with a chemical purity of 99.9% (achiral analysis) and an enantiomeric excess of 46% (chiral analysis), meaning that a significant amount of racemic lansoprazole was still present in the sample. *See, e.g.,* TX 0301 (Larsson II) at TX 0301-0010, col.18, ll.26-29; Trial Tr. (Rogers Cross) 613:6-614:1.

172. This residue was dissolved in acetonitrile and a precipitate was removed by filtration. TX 0301 (Larsson II) at TX 0301-0010, col.18, ll.27-31. In the final step of the purification, "[e]vaporation of the filtrate afforded an oil with enhanced optical purity. Repeating this

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procedure a couple of times afforded 0.31 g (14%) of the desired compound as an oil with an optical purity of 99.6% e.e." *Id.* at col.18, ll.30-35; *see also* Trial Tr. (Atwood Direct) 906:18-24 ("Larsson in Example 22 prepares an oil . . . which is highly chemically and optically pure."); *id.* at 921:1-5 ("Larsson obtained, . . . after three extractions with acetonitrile, 99.6% EE.").

173. Thus, although Larsson was able to obtain crystals of enantiomers of omeprazole and compounds (Ib), (Ic), and (Ie) and solids of compounds (Ib), (Ic), and (Ih), the Court finds that Larsson did not isolate any solid – crystalline or amorphous – of lansoprazole or its enantiomers. *See, e.g.*, Trial Tr. (Atwood Direct), at 905:13-24, 906:18-21 (indicating that Larsson made a pure dexlansoprazole oil but that solid dexlansoprazole had not been accomplished); *see also id.* (Rogers Direct), at 500:17-19 (indicating that the dexlansoprazole isolated in Larsson is an oil); *id.* (Genck Direct) 735:1-5 (same).

174. Although Larsson contains some general language indicating that some of the crude products of the asymmetric oxidation reactions it discloses can be crystallized, *see* TX 0301 (Larsson II) at TX 0301-0006, col.10, ll.28-33, the specific examples in Larsson demonstrate that crystals will not always result.

b. Von Unge

175. Von Unge does not disclose the asymmetric synthesis of enantiomers, but rather discloses a process for improving the optical purity of enantiomerically enriched compounds (that is, compounds that contains more of one enantiomer than the other), including enantiomers of the following compounds: omeprazole (formula Ia); lansoprazole (formula Ib); pariprazole (formula Ic); leminoprazole (formula Id), and the related compound 2-[(4-methoxy-6,7,8,9-tetrahydro-5H-cydohepta[b]pyridin-9-yl)sulphinyl]-1H-benzimidazole(formula Ie). *See* TX 0302 (Von Unge II), at TX 0302-0002 -0003, col.2, l.65-col.4, l.50; Trial Tr. (Atwood Direct), at 951:11-21.

176. The processes disclosed in Von Unge involve dissolving the enantiomerically enriched compound in an organic solvent referred to by Von Unge as the mother liquor. TX 0302 (Von Unge II) at TX 0302-0002 to -0003, col.2, l.65 to col.4, l.50. Von Unge discloses that the racemic compound will precipitate or crystallize from the mother liquor, leaving in solution an even greater enantiomeric excess of the desired compound. *Id.* Once the racemate has precipitated, the

solvent in the mother liquor is removed by evaporation. As a result, "[a] dramatic[] enhancement of the enantiomeric excess of the (-)-enantiomer or the (+)-enantiomer of the present compounds is obtained in the mother liquor (filtrate), even after only one racemate crystallisation." *Id.* at TX 0302-0003, col.4, ll.33-36.

177. Von Unge, the sole inventor of the Von Unge reference, was a named inventor on the Larsson patent. The Von Unge reference discloses several examples of the enantiomeric enrichment of omeprazole and a few examples with other compounds including lansoprazole, pariprazole, and leminoprazole. *See id.* at TX 0302-0003 to -0006. Example 12 discloses the enantiomeric enrichment of (R+)-lansoprazole. The teachings of Von Unge with regard to dexlansoprazole are for all relevant purposes identical to those of the Larsson reference. *See id.* at TX 0302-0006, col.9, ll.20-31; Trial Tr. (Rogers Direct), at 600:1-5; *see also id.* (Genck Direct) 738:9-18. Example 12 is largely identical to Example 22 in Larsson. *See* Trial Tr. (Genck Cross) 838:1-18 (indicating that Von Unge Example 12 "describes, essentially, the same final steps as are described in Example 22 of Larsson"); *id.* (Atwood Direct) 951:11-21 (indicating that "Von Unge essentially describes the same acetonitrile steps as were disclosed in Example 22 of Larsson"); *see also id.* (Rogers Direct) 600:6-17 (noting that Von Unge Example 12 is similar to Larsson Example 22). As in Larsson, a small amount of (R+)-lansoprazole with an enantiomeric excess of 46% was dissolved in acetonitrile. *See* TX 0302 (Von Unge), at TX 0302-0006, col.9, ll.25-27; Trial Tr. (Rogers Direct) 600:6-17. Racemic lansoprazole precipitated from the mother liquor. *See* TX 0302 (Von Unge), at TX 0302-0006, col.9, ll.25-28; Trial Tr. (Rogers Direct) 600:6-17. Again, as in Larsson, after the precipitate was removed by filtration, "[e]vaporation of the filtrate [i.e., the mother liquor] afforded an oil with enhanced optical purity. Repeating this procedure a couple of times afforded 0.31 g of the desired compound as an oil with an optical purity of 99.6% e.e." *Id.* at col.9, ll.27-31; *see also* Trial Tr. (Rogers Direct) 600:6-17; *id.* (Atwood Direct) 921:1-5 ("Larsson obtained . . . after three extractions with acetonitrile 99.6% EE.").

178. Thus, Von Unge, like Larsson, teaches the synthesis of (R+)-lansoprazole as an oil but not a solid. *See, e.g.*, Trial Tr. (Genck Cross) at 838:14-18.

c. Barberich

179. The Barberich reference discloses solid pharmaceutical compositions of dexlansoprazole. For example, in the course of describing various pharmaceutical compositions with dexlansoprazole, Barberich states that "[c]ompressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules." TX 0078 (Barberich II) at TX 0078-0005 [0035].

180. Barberich further states that "the optically pure (+) isomer of lansoprazole is a superior agent for treating ulcers of the stomach, duodenum, and esophagus, gastroesophageal reflux diseases, Zollinger-Ellison Syndrome and other disorders, including those that would benefit from an inhibitory action on H+,K+-ATPase in that it provides this effective treatment while substantially reducing the adverse effects of racemic lansoprazole . . . ." *Id.* at TX 0078-0003 [0015].

181. Despite Barberich's disclosure of solid pharmaceutical compositions of dexlansoprazole, nothing in Barberich teaches the skilled person how to synthesize any solid form of dexlansoprazole, let alone a crystal. *See, e.g.,* Trial Tr. (Atwood Direct) at 899:10-25 (stating that "[t]he Barberich reference really provides no guidance or direction in [] regard [to how one could make a solid form of dexlansoprazole."). None of the working examples discusses using a crystal of dexlansoprazole, and the word "crystal" does not appear in the Barberich reference.

182. Barberich merely incorporates by reference the synthesis methods disclosed in the Larsson and Von Unge references (as well as another reference by Graham, which Defendants do not rely upon) in the following paragraph on page 2:

> Syntheses of R(+) lansoprazole and S(-) lansoprazole by asymmetric oxidation and by bioreduction are described in PCT applications WO 9602535 and 9617077, respectively, the disclosures of which are incorporated herein by reference. The enrichment of single enantiomers by crystallization of the racemate from non-racemic mixtures is described in PCT application WO 97/02261, the disclosure of which is also incorporated herein by reference.

TX 0078 (Barberich II) at TX 0078-0003 [0013]. As noted above, WO 96/02535 is Larsson I (TX 0070), and WO 97/02661 is Von Unge I (TX 0071).

183. In his trial testimony, Dr. Genck opined that Barberich teaches that dexlansoprazole can be

combined with pharmaceutically acceptable carriers and therapeutic ingredients and would be known to be superior to the (S-)-enantiomer for use in a pharmaceutical composition. *See* Trial Tr. (Genck Direct) 772:14-773:2; 786:7-787:7.

184. Dr. Genck's opinion that Barberich teaches that the R enantiomer (dexlansoprazole) is superior to the S enantiomer of lansoprazole was undermined by evidence offered by Takeda that on the same day that the Barberich I application was filed, the inventors listed on the Barberich I and II references also filed an international patent application directed toward solid pharmaceutical compositions containing the (S-) enantiomer of dexlansoprazole. *See* WO 99/38512 (TX 0072) (hereinafter "Barberich S-Enantiomer Application") at TX 0072-0001. The Barberich S-Enantiomer Application indicates that the S enantiomer is a "superior agent" for treating the same symptoms. TX 0072 (Barberich S-Enantiomer Application) at TX 0072-008, l. 225 to TX 0072-009 l. 15. While the two applications cast doubt on Dr. Genck's testimony that Barberich taught that the R enantiomer was considered superior to the S enantiomer, a close reading of the two Barberich applications makes clear that there is, in fact, no real inconsistency between them. In fact, the cited passages do not compare the R and S isomers to each other but rather, both references compare the isolated lansoprazole isomer (whether R or S) to the racemic lansoprazole. In other words, the Barberich applicants apparently concluded that both the R enantiomer and the S enantiomer were superior for treating GERD as compared to racemic lansoprazole.

185. To summarize, Larsson and Von Unge, the primary references relied on by Dr. Genck, disclose dexlansoprazole in oily form only. Barberich, which incorporates Larsson and Von Unge by reference, also does not teach a person of ordinary skill in the art how to make a crystalline form or any solid form of dexlansoprazole.

vii. Katsuki, Tanaka, Borner, Erlandsson

186. The Katsuki, Tanaka and Borner references each disclose the separation of dexlansoprazole from racemic lansoprazole via High Pressure Liquid Chromatography ("HPLC"). Trial Tr. (Genck Direct) 742:5-745:15; *id.* (Atwood Cross) 983:13-15; TX0073 (Katsuki) at 612; TX0069x48 (Tanaka) at 615; TX0075 (Borner) at 174-75. Erlandsson discloses higher-capacity

chiral HPLC columns for separating greater quantities of enantiomers of proton pump inhibitors in the same family of compounds as dexlansoprazole. *See, e.g.*, TX0069x49 (Erlandsson) at 307; Trial Tr. (Genck Direct) 746:2-747:5. According to Erlandsson, the columns can be "easily and inexpensively prepared using published methods." TX0069x49 (Erlandsson) at 307.

c. Prior Art Cited by Impax for Disclosure of Crystallization Methods

i. Tietze, Vogel, Gordon

187. The Tietze, Vogel and Gordon references are textbooks and manuals from the 1970s and 1980s that disclose crystallization techniques and solvents known in the art, which both Drs. Genck and Atwood agreed were familiar to persons of ordinary skill without the need to even consult the textbooks. Trial Tr. (Genck Direct) 747:6-748:6; *id.* (Atwood Cross) 964:22-965:6, 986:20-987:1.

188. For example, Tietze describes the slow cooling of a hot, saturated solution, as well as the dropwise addition of an anti-solvent to a saturated solution of the compound at room temperature to obtain crystals. Trial Tr. (Genck Direct) 748:13-749:16; TX0080 (Tietze) at 24.

189. Tietze and Vogel also disclose techniques that should be attempted if crystallization does not occur spontaneously, including seeding, scratching the flask with a glass rod, and cooling to very cold temperatures and slowly warming the solution. TX0080 (Tietze) at 25; TX0081(Vogel) at 141-42.

190. Vogel also discloses particular methods to be used when inducing crystallization from the oil form. TX0081 (Vogel) at 142; Trial Tr. (Genck Direct) 753:17-756:1.

191. In addition, Tietze advises persons of ordinary skill that "[c]rystallization trials require skill and patience. Several solvents should always be tried," and Vogel echoes this advice by stating that "[t]he exercise of considerable patience is sometimes necessary so as to give the solute every opportunity to crystalli[z]e." TX0080 (Tietze) at 25; TX0081 (Vogel) at 142; Trial Tr. (Genck Direct) 750:17-751:22.

192. The Gordon reference is a chemistry handbook from 1972 that discloses a list of common solvents useful in obtaining crystals. TX0082 (Gordon) at 442-43; Trial Tr. (Genck Direct) 756:17-758:16.

193. Gordon discloses the combination of acetonitrile and diethyl ether (used in Example 1 of the '058 patent), acetone and water (used in Example 2 of the '058 patent), and heptane and ethyl acetate (used in Reference Example 4 of the '058 patent). *Id.* Tietze and Vogel disclose common crystallization solvents as well, including acetonitrile and diethyl ether (used in Example 1 of the '058 Patent) and acetone and water (used in Example 2 of the '058 Patent). TX0080 (Tietze) at 25; TX0081 (Vogel) at 137-38; Trial Tr. (Genck Direct) 749:17-750:16, 752:4-753:16.

194. Tietze and Vogel also contemplate that crystallization does not occur spontaneously, and that in such instances a crystal seed may be needed. *See* TX0080 (Tietze) at 25 ("a few crystals are saved from each crystallization for future use"); TX 0081 (Vogel) at 141 (describing how to gather seed crystals).

195. Further, while Tietze, Vogel and Gordon list a number of known crystallization solvents, they also each acknowledge that crystallization can be difficult and unpredictable. *See, e.g.*, TX 0080 (Tietze) at 25 ("Crystallization trials require skill and patience. Several solvents should always be tried."); TX0081 (Vogel) at 137 (listing generalizations to assist in the selection of a crystallization solvent, but noting that "numerous exceptions are known"); *id.* at 138 ("In practice the choice of a solvent for recrystallization must be determined experimentally if no information is already available."); TX00082 (Gordon) at TX 0082-0003 to TX 0082-0004 (listing common solvents for crystallization, but noting that, "[i]n choosing a second solvent for a mixture, trial and error are usually required").

196. Dr. Genck testified that Tietze, Vogel and Gordon gave general guidance to one skilled in the art at the time of the invention as to how to perform crystallization. *See* Trial Tr. (Genck Direct) 747:6-13. He also testified that some of the methods disclosed in Vogel for obtaining a crystal from an oil, such as scratching the inside of the vessel with a glass rod, seeding the solution, freezing a mixture, and adding solid carbon dioxide, might be used to crystallize dexlansoprazole, but he admitted that he was unaware of any attempts to do so. Trial Tr. (Genck Cross) 841:22-843:2.

ii. Kato, Nohara, Kohl and Bohlin

197. Kato describes methods for crystallizing racemic lansoprazole and a specific method that

produces solvent-free (i.e., anhydrous) crystals of racemic lansoprazole, but not its enantiomers. *See also* Trial Tr. (Genck Direct) 774:6-775:1.

198. Kato demonstrates the unpredictability of crystallization of related benzimidazole compounds. Kato cites a prior art method for crystallizing racemic lansoprazole that resulted in a lansoprazole crystal in monoethanolate monohydrate form (i.e., a solvate containing 1 molecule each of ethanol and water). *See* TX 0069x32 (Kato II) at TX 0069x32-0003, col.1, ll.47-57; *see* also Trial Tr. (Genck Cross) 860:3-17. This prior art method used ethanol and water as a solvent. *See* TX 0069x32 (Kato II) at TX 0069x32-0003, col.1, ll.26-40, 47-57. This monoethanolate monohydrate crystal decomposed easily during vacuum drying, particularly under heating. *See id.* col.1, ll.47-57.

199. Kato discloses that "suspending and stirring the [monoethanolate monohydrate] crystals [of racemic lansoprazole] in warm water . . . unexpectedly causes a transformation of said solvate crystals into substantially solvent-free [i.e., anhydrous] crystals." *Id.* col.2, ll.9-21; *see also id.* (indicating that this desolvation occurred "to everybody's surprise"); *id.* at TX 0069x32-0007, col.10, ll.7-31 (Example 1) (disclosing the preparation of substantially solvent-free racemic lansoprazole crystals by suspending and stirring monoethanolate monohydrate lansoprazole crystals (which were crystallized from ethanol and water, as described in a reference example) in water)); Trial Tr. (Atwood Direct) 969:24-970:4, 970:14-18; *id.* (Genck Cross) 860:21-861:1. Kato further notes that that "[t]he inventors further discovered to their own surprise that the substantially solvent-free crystals of [racemic lansoprazole] . . . are remarkably stable as compared with the conventional [] solvate and completely free from decomposition in the course of vacuum drying." TX 0069x32 (Kato II) at TX 0069x32-0003, col.2, ll.21-26.

200. Nohara (TX 0097) likewise describes only the crystallization of racemic compounds, including the crystallization of racemic lansoprazole. *See* TX 0097 (Nohara); *see also* Trial Tr. (Genck Cross) 847:7-16; *id.* (Atwood Direct) 966:17-967:1.

201. Kohl (TX 0086) discloses a process for separating omeprazole, pantoprazole, and related compounds into their enantiomers using highly-concentrated mineral acids. *See* TX 0086 (Kohl) at TX0086-0007.

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202. Examples 1 and 2 of Kohl together disclose the synthesis of crystals of (+)-pantoprazole from a racemic pantoprazole salt. *See id.* at TX 0086-0006; *see also* Trial Tr. (Genck Direct) 761:9-762:13; *id.* (Genck Cross) 853:9-24. Example 1 discloses the synthesis of an intermediate compound from racemic pantoprazole. *See* TX 0086 (Kohl) at TX 0086-0006; *see also* Trial. Tr. (Genck Cross) 853:9-854:20. This intermediate, which Dr. Genck surmised to be a crystal, was then used as the starting material in Example 2 for the synthesis of the enantiomer, (+)-pantoprazole, as an oil using sulfuric ac*id. See id.*; Trial Tr. (Genck Cross) 854:3-25; *see* TX 0086 (Kohl) at TX 0086-0006; Trial Tr. (Genck Direct) 761:15-762:8. Subsequently, crystals were formed from the oil by crystallization using diisopropyl ether as a solvent. *See* TX 0086 (Kohl) at TX 0086-0006; Trial Tr. (Genck Direct) 761:15-762:8. Kohl does not disclose any measurement of the optical purity of the resulting (+)-pantoprazole. *See* TX 0086 (Kohl) at TX 0086-0006.

203. In Example 6, Kohl discloses the use of the procedure described in Example 2 to isolate the (R+) enantiomer of omeprazole. *See* TX 0086 (Kohl) at TX 0086-0007; Trial Tr. (Genck Cross) 855:22-866:17. However, in Example 6 the procedure described in Example 2, which was reported to result in the synthesis of crystals of (+)-pantoprazole in that example, led to the synthesis of (R+)-omeprazole as an amorphous solid, and produced no crystals of (R+)-enantiomer. *See* TX 0086 (Kohl) at TX 0086-0007; Trial Tr. (Atwood Direct) 965:13-16 ("Kohl obtains crystals of pantoprazole. And he tried to obtain crystals of R-omeprazole, but he failed to do so."); *id.* (Genck Cross) 855:22-866:17.

204. Bohlin (TX 0076) discloses the synthesis of S-omeprazole in three different forms, obtained three different ways: an amorphous solid form, a partially crystalline/partially amorphous form, and a fully crystalline form. *See* Trial Tr. (Atwood Direct) 965:22-966:12. The procedures described in Bohlin are complicated and start from a sodium salt of S-omeprazole. *See id.* at 966:8-12. First, Bohlin discloses a method for preparing amorphous solid esomeprazole that involves starting with a sodium salt of S-omeprazole and acid treatment followed by "evaporating a solution of neutral S-omeprazole in one or more organic solvents to a highly concentrated solution, adding a further solvent to the highly concentrated solution and evaporating further until solid amorphous neutral S-omeprazole is formed." TX 0076 (Bohlin) at TX 0076-0006, ll.14-16;

id. at TX 0076-0011, l.19 to TX 0076-0012, l.2 (Example 1). Bohlin then discloses "crystallization from a solution of S-omeprazole in one or more organic solvents and optionally water," including crystallization of S-omeprazole from amorphous solid (Examples 2-8) or partially crystalline (Example 9) S-omeprazole using various solvents. *Id.* at TX 0076-0006, ll.18-19; *see id.* at TX 0076-0012 to TX 0076-0014 (Examples 2-9). Finally, Bohlin discloses "precipitation from a solution of an alkaline salt of S-omeprazole in water and, optionally one or more organic solvents, with a suitable acid" and the use of this technique to generate a partially crystalline form of S-omeprazole. *Id.* at TX 0076-0006, ll.21-22; *see id.* at TX 0076-0014 to TX 0076-0015 (Examples 10-11).

205. Bohlin does not disclose the preparation of a solid or crystal of any benzimidazole compound other than S-omeprazole.

d. Whether a Person of Ordinary Skill in the Art Would have been Motivated to Obtain a Crystal of Dexlansoprazole

206. The evidence presented at trial supports the conclusion that a person of ordinary skill in the art would have had a reason to attempt to obtain a crystal form of dexlansoprazole.

207. First, a person of ordinary skill in the art would have been motivated to select dexlansoprazole for use as a pharmaceutical. Trial Tr. (Genck Direct) 771:2-6; *id.* (Atwood Cross) 1010:1-4. As of June 1999, it was known that racemic lansoprazole was effective as an inhibitor of gastric acid secretion, indicating to persons of ordinary skill in the art that its enantiomers would likely have the same benefits. TX0070, Larsson I at 1; TX0071, Von Unge I at 1; Trial Tr. (Genck Direct) 771:13-772:13; *id.* (Rogers Direct) 596:6-19; *id.* (Atwood Cross) 1010:1-4. Moreover, Barberich had identified dexlansoprazole as having advantages over the racemic lansoprazole for treating gastroesophageal reflux disease. TX0078, Barberich at [0015]. Indeed, Takeda's expert, Dr. Atwood, testified that "it was also known by June of 1999 that dexlansoprazole was effective to treat GERD" and that although "[t]here was a little bit of controversy with regard to the Barberich reference, as to whether R or S was more effective . . . [his] understanding was that R was more effective." Trial Tr. (Atwood Cross) 985: 3-8. To the extent there was any question as to whether the R or the S enantiomer was likely to be more

effective, a person of ordinary skill would have understood that *both* would have advantages over the racemic lansoprazole for the treatment of GERD.

208. Second, it was known as of June 1999 that crystalline forms are preferred in the pharmaceutical context because they are more stable, have a higher degree of purity, and are easier to process into pharmaceutical compositions. Trial Tr. (Genck Direct) 714:19-715:7, 804:7-11; *id.*. (Rogers Cross) 700:9-13; *id.* (Atwood Direct) 896:16-22; TX0076 (Bohlin) at 2 (crystals are preferred to oils). Takeda's expert, Dr. Atwood, agreed that if a person of ordinary skill in the art had an oil of dexlansoprazole (as disclosed by Larsson and Von Unge) and sought to use it as a pharmaceutical, he or she would have been motivated to crystallize it. Trial Tr. (Atwood Cross) 990:14-18.[4]

e. Whether a Person of Ordinary Skill in the Art Would Have a Reasonable Expectation of Success

209. While a person of skill in the art would have had a reason to attempt to obtain any crystal form of dexlansoprazole, the prior art would not have given rise to a reasonable expectation of success as to that objective.

i. Prior Art Disclosing Asymmetric Oxidation to Obtain Dexlansoprazole

210. A person of ordinary skill in the art would not have a reasonable expectation of success that a crystal of dexlansoprazole could be obtained, or that the anhydrous crystal of claim 1 of the

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[4] Dr. Genck testified further that a person of ordinary skill in the art would have been especially motivated to make the anhydrous crystalline form of dexlansoprazole. Trial Tr. (Genck Direct) 773:23-775:10. The Court does not find Dr. Genck's testimony on this point persuasive. Dr. Genck based his opinion on Kato, which teaches that the anhydrous crystalline form of the racemic lansoprazole was remarkably stable as compared to its solvates, including hydrates. TX0087, Kato at 3:22-27; Trial Tr. (Genck Direct) 774:12-775:3 ; *id.* (Atwood Cross) 992:2-6. However, Dr. Genck provided no evidence or explanation to support his position that the stability of a given crystal form of a racemic molecule is predictive of the stability of or the ability to crystallize an enantiomer. By his own admission, Dr. Genck is not a specialist in organic chemistry or in the differences among the structures of benzimidazole compounds. See *id.* (Genck Cross) 837:4-14. Dr. Atwood, who is an expert in organic chemistry as well as crystallization, testified that the crystallization of a racemic compound is not predictive of and can be vastly different from the crystallization of a specific enantiomer of that compound, as discussed further below. Accordingly, the Court finds that the disclosures in Kato did not provide one of skill in the art at the time of Takeda's invention with motivation to generate dexlansoprazole in anhydrous crystal form.

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'058 Patent could be obtained, based on Larsson or Von Unge. As set forth below, the Court finds that Larson and Von Unge sought to produce crystals of dexlansoprazole and that their failure to achieve this result would have demonstrated to a person of ordinary skill in the art the difficulty of crystallizing the dexlansoprazole molecule.

211. The Larsson inventors were scientists at Astra – the company that discovered omeprazole and esomeprazole – and were also responsible for the discovery that the large-scale synthesis of esomeprazole and related compounds could be achieved using asymmetric oxidation followed by crystallization, as described in the Larsson and Von Unge patents. *See* TX 0236 (Cotton); TX 0070 (Larsson I); TX 0301 (Larsson II); Trial Tr. (Atwood Direct) 944:20-945:5 ("[T]he emphasis in Larsson . . . . was to do the oxidation to get the enantioselective synthesis on an industrial scale, on a scale useful to industry . . . ."). The Larsson patent itself teaches the asymmetric synthesis of a large amount of an enantiomer of the salt of omeprazole using close to 7 pounds of oxidant. *See id.*; TX 0301 (Larsson II) at TX 0301-0008, col.13, l.51 to col.14, l.13 (Example 11). As Dr. Atwood testified, considerable skill and expertise is needed to perform such a reaction on such a large scale. *See* Trial Tr. (Atwood Direct) 945:6-946:14. Further, many of the inventors listed on Larsson I and Larsson II, especially Larsson, Von Unge, and Cotton, are named inventors on numerous patents and authors of numerous scientific publications. *See* Trial Tr. (Atwood Direct) 945:6-946:14. One skilled in the art reasonably would conclude from the fact that the Larsson inventors' stated goal was to synthesize large quantities of compounds for pharmaceutical compounds, *see* TX 0301 (Larsson II) at TX 0301-0002, col.1, ll.23-55, and the fact that they successfully synthesized other compounds as crystals, that Larsson and Von Unge sought to produce a crystal form of dexlansoprazole but failed.

212. Indeed, Larsson describes the synthesis of dexlansoprazole with high chemical purity (99.9% achiral analysis) and high optical purity (99.6% e.e.). After treating this residue with acetonitrile Larsson obtained only an oily form of dexlansoprazole. *See* TX 0301 (Larsson II) at TX 0301-0010, col.18, ll.30-35; *see also* Trial Tr. (Atwood Direct) 905:13-24, 906:18-21; *id.* (Rogers Direct) 500:17-19; *id.* (Genck Direct) 735:1-5. Repeating the procedure "a couple of times" did not even result in a solid form of dexlansoprazole, let alone a crystal. *See* TX 0301

(Larsson II) at TX 0301-0010, col.18, ll.30-35. Furthermore, Dr. Atwood testified that the technique used in Example 22 in Larsson, in particular the "[e]vaporation of the filtrate [which] afforded an oil with enhanced optical purity," described in Example 22 at lines 31-33, was the crystallization technique of crystallization by evaporation. As Larsson discloses, the solvent, acetonitrile, was evaporated even though this crystallization technique was unsuccessful in yielding crystals and resulted in an oil. *See* Trial Tr. (Atwood Direct) 947:15-949:8. Larsson thus would have led a person skilled in the art to expect that using acetonitrile as a solvent (the solvent that Dr. Kamiyama ultimately used together with diethyl ether, to successfully obtain crystalline dexlansoprazole for the first time) was not likely to result in crystallization.

213. Moreover, as acknowledged by Dr. Genck, Example 23 in Larsson discloses the synthesis of crystals of an enantiomer of another benzimidazole compound using acetonitrile as a solvent. *See* TX 0301 at TX 0301-0010, col.18, ll.37-67; Trial Tr. (Genck Cross) 836:22-24. Although the two Examples do not describe the crystallization in exactly the same words, as Dr. Atwood testified, one skilled in the art would understand that the same crystallization process was used in Examples 22 and Example 23 – heating and then evaporating the solution containing the solvent and compound of interest – but yielded completely different results. Trial Tr. (Atwood Direct) 947:17-949:8. Thus, the Court finds that Larsson discloses a failure to crystallize dexlansoprazole using acetonitrile as a solvent and the successful crystallization of an enantiomer of another benzimidazole compound using the same solvent. Therefore, the Court further finds that at the time of the Takeda inventions, successful crystallization of benzimidazole compounds, such as dexlansoprazole, from a given solvent, such as acetonitrile, was not predictable.

214. Von Unge's goal was also to isolate enantiomers of omeprazole and related compounds for use in pharmaceutical products. TX 0302 (Von Unge II) at TX 0302-0001, col.1, ll.24-67. Nevertheless, Von Unge, like Larsson, was able to isolate the R- and S-enantiomers of lansoprazole only as oils, despite repeating the acetonitrile procedure "a couple of times." *Id.* at TX0302-0006, col.9, ll.9-19 (Example 11) ((S-)-lansoprazole); *id.* at TX 0302-0006, col.9, ll.20-31 (Example 12) (dexlansoprazole); *see also* Trial Tr. (Genck Cross) 838:14-18. Moreover, in Examples 11 and 12, it is the racemic compound that precipitates out of solution, not the desired

enantiomers. TX 0302 (Von Unge II) at TX0302-0006, col.9, ll.9-19 (Example 11) ((S-)-lansoprazole); *id.* at TX 0302-0006, col.9, ll.20-31 (Example 12) (dexlansoprazole).

215. Although Impax's expert, Dr. Genck, testified at trial that neither Larsson nor Von Unge (which, as noted above, have essentially the same disclosures relating to dexlansoprazole) attempted to crystallize dexlansoprazole, this testimony was inconsistent with his deposition testimony, which he reaffirmed at trial, that Von Unge was in fact "about crystallization" (as well as enantiomeric enrichment) and that "[Von Unge] did one; one solvent; one attempt." Trial Tr. (Genck Cross) 838:19-839:24. This supports the Court's finding that, as Dr. Atwood testified, both Larsson and Von Unge represent unsuccessful efforts to crystallize dexlansoprazole using acetonitrile as a solvent.

216. Thus, although Larsson and Von Unge disclose dexlansoprazole in oily form, they support the conclusion that a person of ordinary skill in the art would not have had a reasonable expectation that dexlansoprazole could be crystallized based on the prior art of that time. As Barberich merely incorporates Larsson and Von Unge, that prior art supports the same conclusion.

ii. Prior Art Disclosing HPLC to Obtain Dexlansoprazole

217. Similarly, a person of ordinary skill in the art would not have a reasonable expectation of success that a crystal of dexlansoprazole could be obtained, or that the anhydrous crystal of claim 1 of the '058 Patent could be obtained, based on the prior art cited by Impax disclosing the separation of lansoprazole enantiomers using HPLC.

218. First, the person of ordinary skill in the art in 1999 would not understand from Katsuki, Tanaka, and Erlandsson how to isolate dexlansoprazole, because none of these references discloses the isolation of dexlansoprazole. *See* Trial Tr. (Atwood Direct) 962:1:5 (stating that Katsuki and Tanaka do not "disclose isolating dexlansoprazole out from the solvent coming out of the HPLC column"); *id.* (Genck Cross) 843:3-15 (indicating that Katsuki and Tanaka relate to HPLC on lansoprazole but Erlandsson pertains to "omeprazole, a different compound"); *see also id.* (Atwood Direct) 963:8-12 (indicating that Erlandsson discloses separation of enantiomers of omeprazole); TX 0069x49 (Erlandsson) (disclosing enantiomeric separation of omeprazole but not lansoprazole). Likewise, none of these three references discusses or teaches crystallization. Trial

Tr. (Atwood Direct) 961:21-25. Thus, none of these references would have suggested to a person of ordinary skill in that art that HPLC could be used to make dexlansoprazole for crystallization.

219. Further, the HPLC method disclosed by Katsuki does not include the additional steps that would have to be taken to isolate dexlansoprazole for crystallization. Dr. Atwood explained in his trial testimony that there are two ways to perform HPLC. *See id.* at (Atwood Direct) 955:21-966:8. First, analytical HPLC, the technique used by Katsuki, is used to detect the mere presence of a material, and is so sensitive that it can detect a few parts per million of the compound coming through the column. *See id.* at 951:21-956:20. An analytical HPLC column, such as the one Katsuki used, has a width about the size of a pen. *See id.* at 954:4-17. The interior containing the matrix that has an affinity for the compound and delays its travel through the column is about four millimeters in diameter, and the column is about a foot in length. *See id.* Thus, the section of material is very thin. *See id.* The second type of HPLC is preparative HPLC, typically uses a larger column, such as a column that is about one or two inches in diameter, and is "designed specifically not for detecting the material, but for separating two or more materials, one from another." *Id.* at 956:9-20.

220. Katsuki says nothing about preserving the fractions containing the enantiomers for further experiments. Dr. Atwood testified that he was unaware of any instances where analytical HPLC was used to isolate solid compounds for the purposes of crystallization. He noted that it would be difficult to obtain enough material for crystallization, as the solution containing the compound eluted from the column contains a miniscule amount of the separated compound diluted within a large volume of solvent. *See id.* at 956:21-957:5, 962:12-21. Given the dilute nature and small amount of the dexlansoprazole obtained in the HPLC fractions in these references, they do not disclose separation of dexlansoprazole in a form that would constitute an adequate starting material for known crystallization methods.

221. Thus, even if Katsuki disclosed the collection of the enantiomeric fractions, which, as discussed above, it does not, (R+)-lansoprazole would be in solution at the end of the process, so additional steps would be required to isolate dexlansoprazole from the solvent in order to prepare crystalline forms of (R+)-lansoprazole. Katsuki, however, does not "disclose isolating

dexlansoprazole from the solvent coming out of the HPLC column." Trial Tr. (Atwood Direct) 962:1-5; *see also id.* (Genck Cross) 844:4-6.

222. The '058 Patent teaches that preparative HPLC can be used to isolate material that can be used in crystallization. The'058 Patent discloses amorphous dexlansoprazole obtained from chiral preparative HPLC as the starting material for the disclosed crystallization. *See* Trial. Tr. (Atwood Direct) 967:6-16; TX 0001 ('058 Patent) at TX 0001-0005, col.7, ll.31-52 (Reference Example 1); TX 0001-0006, col.8, ll.27-51 (Example 1). Based upon this fact, Dr. Genck opined that one skilled in the art would also have been motivated to obtain dexlansoprazole as starting material for crystallization using HPLC (either preparative HPLC, or, as Takeda did, multiple runs of analytical HPLC). *See* Trial Tr. (Genck Direct) 741:11-743:11, 744:22-745:15.

223. However, as noted above, Katsuki does not "disclose isolating dexlansoprazole from the solvent coming out of the HPLC column." *Id.* (Atwood Direct) 962:1-5. Thus, one skilled in the art would need to perform additional steps to isolate dexlansoprazole from the solvent and prepare a material suitable for use in crystallization. Further, dexlansoprazole is unstable in solution and decomposes. *See id.* (Kamiyama Direct) 105:20-107:12. The inventors of the '058 Patent accordingly had to treat the dexlansoprazole material they obtained after HPLC separation to prevent its decomposition. *See id.* (Atwood Direct) 961:3-7. They did so by adding hexane to the material while it was being concentrated in solution after the HPLC separation in Reference Example 1. *See id.* at 961:8-20; *see also* TX 0001 ('058 Patent) at TX 0001-0005, col.7, ll.31-52 (Reference Example 1) (indicating the addition of hexane). Dr. Atwood testified that the prevention of decomposition of dexlansoprazole by the addition of hexane was unpredictable before it was done by the inventors of the '058 Patent. *See* Trial Tr. (Atwood Direct) 961:12-18.

224. Similarly, in Reference Example 2 in the '058 Patent, which also discloses the isolation of dexlansoprazole by HPLC for use in crystallization experiments, the inventors also used triethylamine to prevent decomposition of dexlansoprazole after HPLC in concentrated solution *See* TX 0001 ('058 Patent) at TX 0001-0005, col.7, l. 54 to col.8, l.5 (Reference Example 2) (disclosing the addition of triethylamine); TX-00001-0007, col.11, l.11 to col.12, l.27 (Examples 2 and 3) (disclosing the crystallization of the dexlansoprazole material described in Reference

Example 2); cf. Trial. Tr. (Kamiyama Direct) 106:18-108:4 (indicating that triethylamine was added to prevent degradation of dexlansoprazole in solution); TX 0722 (SSCI document entitled "Standard Polymorph Screen") at TX 0722-0002 ("TAK-390 [dexlansoprazole] degraded in solution over time but was stabilized by addition of triethylamine."). Because Katsuki was not concerned with any post-HPLC processing of the dexlansoprazole he separated, he neither mentioned the tendency of dexlansoprazole to decompose nor disclosed any steps necessary to prevent such decomposition, which would have been a starting point if one wanted to undertake further crystallization procedures.

225. Furthermore, Katsuki does not report the enantiomeric purity of any of the peaks of (+)-lansoprazole. *See, e.g.,* Trial Tr. (Atwood Direct) 962:18-21. Thus, one skilled in the art would not know whether the fractions were of sufficient purity to provide adequate conditions for crystallization of the enantiomer, given that, as discussed above, impurities can prevent crystallization. *See id.* at 949:9-23; *cf. id.* at 962:22-963:7 (indicating that "before attempting to crystallize something, one would want to know the level of impurity – the level of purity that one had in the final product"). This is especially true given that Katsuki's starting material was blood serum, which contained a huge array of biological impurities. *Cf. id.* at 962:22-963:7. Accordingly, the Court rejects Dr. Genck's conclusion that one of ordinary skill in the art would have had a reasonable expectation that the technique disclosed in Katsuki could be used successfully to isolate dexlansoprazole for crystallization.

226. Like Katsuki, Tanaka (TX 0069x48) discloses analytical HPLC to resolve the enantiomers of lansoprazole. Trial Tr. (Atwood Direct) 955:21-956:8. The same conclusions discussed above in the context of Katsuki, including those with respect to scale-up, also apply to Tanaka with the exception that Tanaka did not involve lansoprazole derived from serum. Dr. Atwood testified that dexlansoprazole obtained in Tanaka was a "very dilute solution," Trial Tr. (Atwood Direct) 962:15-17, and Tanaka also used a 4.6 millimeter column, *see* TX 0069x48 (Tanaka) at TX 0069x48-0003, Trial. Tr. (Genck Direct) 744:4-17, consistent with analytical HPLC. Also, like Katsuki, Tanaka does not "disclose isolating dexlansoprazole out from the solvent coming out of the HPLC column," Trial Tr. (Atwood Direct) 962:1-5; *id.* (Genck Cross) 844:4-6 (admitting that

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"in Tanaka, the separated enantiomers remain in solution"), or the collection of fractions. Nor does Tanaka report the enantiomeric purity of any of the peaks of (+)-lansoprazole. *See, e.g.*, Trial Tr. (Atwood Direct) 962:18-21. Indeed, Tanaka was not even able to identify which enantiomer was coming off of the HPLC column. TX 0069x48 (Tanaka) at TX 0069x48-0005. Accordingly, the Court finds that one of ordinary skill in the art would not have a reasonable expectation that the disclosure in Tanaka would allow such a person to successfully prepare dexlansoprazole for a crystallization attempt, for the same reasons the Court reached this conclusion with respect to the Katsuki reference delineated above.

227. Similarly, the Court finds that one skilled in the art would not read Erlandsson as teaching a means to obtain dexlansoprazole in sufficient purity or amount to perform crystallization. Erlandsson reports the separation of omeprazole into its enantiomers using a cellulose-based chiral column. *See* TX 0069x49 (Erlandsson) at TX0069x49; *see also* Trial Tr. (Atwood Direct) 963:8-12 (indicating that Erlandsson discloses separation of enantiomers of omeprazole). Erlandsson does not describe the separation of lansoprazole at all. *See id.* (Genck Cross) 843:3-15 (indicating that Katsuki and Tanaka relate to HPLC on lansoprazole but Erlandsson pertains to "omeprazole; a different compound"). As Dr. Atwood testified, "the material Erlandsson's getting out after he does chromatography is still quite impure." *Id.* at 963:20-25. The enantiomeric purity of the fractions obtained by Erlandsson was 82% for (+)-omeprazole and 95.6% for (-)-omeprazole, less than that of Larsson and Von Unge. TX 0069x49 (Erlandsson) at TX 0069x49-0014. Given that Erlandsson teaches a technique that resulted in compounds of much lower purity than the dexlansoprazole Larsson obtained in oil form, the Court agrees with Dr. Atwood's opinion that one of ordinary skill in the art would not have concluded from Erlandsson that he or she could use HPLC for purposes of obtaining a compound (e.g., dexlansoprazole) to be used in crystallization experiments. *See id.* (Atwood Direct) 963:14-19.

228. In sum, the HPLC references would not teach one skilled in the art how to make dexlansoprazole for purposes of crystallization or give rise to a reasonable expectation of success in doing so. Nothing in Katsuki, Tanaka or Erlandsson describes (i) concentrating the fractions of dexlansoprazole from the chiral column so as to amass sufficient material to attempt

crystallization, (ii) filtering the dexlansoprazole from the eluate, (iii) obtaining a substance of sufficient purity to be an appropriate candidate for crystallization, or (iv) adding hexane or triethylamine to the resulting filtrate to prevent decomposition. All of these steps were done in preparing the material used in the successful crystallization of dexlansoprazole disclosed in the '058 Patent. *See* TX 0001 ('058 Patent) at TX 0001-0005, col.7, ll.42-46 (Reference Example 1), col.8, ll.9-29 (Reference Example 2).

iii. Prior Art Disclosing Methods of Crystallization

229. Finally, the person of ordinary skill in the art in 1999 would not have had a reasonable expectation of being able to crystallize dexlansoprazole, whether obtained through asymmetric oxidation or by HPLC, using the general crystallization methods known in the art, such as those described in Tietze, Vogel and Gordon, or the specific methods used for crystallizing other benzimidazole compounds described in Kato, Nohara, Kohl and Bohlin. The Court finds that Dr. Genck's opinions based the disclosure of potential solvents and techniques in these references are not credible because they reflect an improper hindsight analysis.

230. Tietze (TX 0080) and Vogel (TX 0081) describe several common crystallization techniques, while Gordon (TX 0082) describes many common solvents used in crystallization. *See* TX 0080 (Tietze); TX 0081 (Vogel); TX 0082 (Gordon). These references do not contain examples of actual crystallizations of benzimidazole molecules, let alone dexlansoprazole. Further, none of these references – or, for that matter, any of the references disclosing crystallization of related compounds – discloses the use of a nitrogen stream during crystallization like that used in the initial crystallization of dexlansoprazole disclosed in Example 1 of the '058 Patent. Accordingly, the particular method that resulted in crystalline dexlansoprazole is not taught by any references upon which Dr. Genck relied.

231. Tietze and Vogel also contemplate that crystallization does not occur spontaneously, and that a crystal seed may be needed to bring about crystallization. *See* TX 80 (Tietze) at TX 0080-0004 ("a few crystals are saved from each crystallization for future use"); TX 81 (Vogel) at TX 0081-0009 (describing how to gather seed crystals). In fact, as discussed above, Dr. Kamiyama did use a crystal seed of the anhydrous crystal of dexlansoprazole from Example 1 of the '058

Patent to encourage crystallization of the sesquihydrate crystals disclosed in Example 3 and Step 2 of Example 2 of the '058 Patent. However, a technique that employs a crystal seed presupposes the existence of a suitable crystal for use in seeding. Here, the inventors necessarily had to obtain the original dexlansoprazole crystal without benefit of any pre-existing crystals to use as a seed. Indeed, as discussed above, Dr. Genck admitted that there were no dexlansoprazole seed crystals available before the first crystallization of dexlansoprazole disclosed in the '058 Patent. *See* Trial Tr. (Genck Cross) 808:14-18. The fact that crystallization sometimes requires the use of a crystal seed to be performed successfully is further indicative of the unpredictable and uncertain nature of crystallization.

232. While the general crystallization references list a number of known crystallization solvents, they also each acknowledge that crystallization can be difficult and unpredictable. *See, e.g.*, TX 0080 (Tietze) at TX 0080-0004 ("Crystallization trials require skill and practice"); TX 0081 (Vogel) at TX 0081-0005 (listing generalizations to assist in the selection of a crystallization solvent, but noting that "numerous exceptions are known"); *id.* at TX 0081-0006 ("In practice the choice of solvent for recrystallization must be determined experimentally if no information is already available"); TX 00082 (Gordon) at TX 0082-0003 to TX 0082-0004 (listing common solvents for crystallization, but noting that, "[i]n choosing a second solvent for a mixture, trial and error are usually required").

233. The methods that Dr. Kamiyama unsuccessfully tried involved solvents mentioned in the textbooks cited as prior art by Impax, namely, Tietze, Vogel and Gordon. *See* TX 0081 (Vogel) at TX 0081-0004 to TX 0081-0005 (identifying THF, methanol, ethanol, ethyl acetate as solvents); TX 0082 (Gordon) at TX 0082-0003 to TX 0082-0004 (identifying methanol, ethanol, ethyl acetate, and hexane as solvents) ; *see also* TX 0080 (Tietze) at TX 0080-0003 to TX 0080-0004 (indicating the use of methanol as a solvent (in conjunction with another solvent) and hexane in conjunction with other solvents). Moreover, as Dr. Genck admitted, developing a crystallization method involves determining "what to do after the solvents are selected," including determining the proportion of the solvents to be used, and the temperature conditions. Trial Tr. (Genck Cross) 819:25-820:8, 820:23-821:5. There are dozens, if not hundreds, of other possible methods and

conditions disclosed in these references that one ordinarily skilled in the art potentially could have used.

234. The inherent unpredictability of crystallization is reflected in the fact that, as Dr. Genck admitted, hundreds of patents have been issued on crystal forms of compounds. *See id.* (Genck Cross) 830:5-15; *See* TX 00576 (J. Keith Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids," in *Polymorphism in Pharmaceutical Solids* (Harry G. Brittain, ed., 1999)) at 64 of 156 (as of 1990, "more than 350 patents on crystal forms granted on the basis of an advantage in terms of stability, formulation, solubility, bioavailability, ease of purification, preparation or synthesis, hygroscopicity, recovery, or prevention of precipitation.").

235. Given the unpredictability of crystallization, absent impermissible hindsight, the lists of potential solvents and solvent combinations set forth in Tietze, Vogel and Gordon would not engender a reasonable expectation of success in any particular method, or in the ability generally to obtain a dexlansoprazole crystal.

236. A reference Dr. Genck relied on in his expert report, but about which he did not testify on direct examination, emphasizes this point. In his expert report, Dr. Genck relied on a reference by Fessenden (TX 0069x12) for common solvents used for crystallization. *See* Trial Tr. (Genck Cross) 815:4-816. The Fessenden reference does not include acetonitrile, either in its table of the 13 most common crystallization solvents or its separate table of common solvent pairs. *See* TX 0069x12 (Fessenden) at TX 0069x12-0006; Trial Tr. (Genck Cross) 816:8-11, 816:22-817:4. Fessenden also lists factors for choosing solvents, including whether the solvent reacts with the compound to be crystallized and solubility of the compound in the solvent, which Dr. Genck admitted would need to be determined through experimentation. *See* TX 0069x12 (Fessenden) at TX 0069x12-0005 ("[u]nfortunately, the solubility of a compound in a solvent cannot be predicted with accuracy"), *see also* Trial Tr. (Genck Cross) 817:5-818:12.

237. Dr. Genck admitted that one would not have any reasonable expectation *a priori* that any particular crystallization method would succeed. He agreed with the statement in Vogel that one does not "know which solvent or combination of solvents is going to succeed in obtaining a crystal" until one does crystallization experiments. Trial Tr. (Genck Cross) 818:17-819:16; *id.* at

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818:13-16 (prior to the '058 Patent "there wasn't information known about which solvents could be used to crystallize dexlansoprazole."). Moreover, he admitted that he could not testify with respect to whether any of the solvent combinations disclosed in the Tietze reference would succeed in crystallizing dexlansoprazole without the teachings of the '058 Patent. *See id.* at 841:4-17. He further acknowledged that he would not have known what particular solvents would have worked with respect to crystallization of dexlansoprazole without performing the experiments. *Id.* at 821:6-19 ("[E]xperiments would be required" to determine this).

238. The Vogel, Gordon, and Fessenden references collectively disclose 36 individual solvents commonly used in crystallization by solution, twelve of which are disclosed in all three sources. Acetonitrile, the solvent Takeda first used to successfully obtain the anhydrous crystal, is not one of the twelve solvents listed by all three sources. Moreover, as both sides' experts testified at trial, crystallization often involves the use of solvent pairs. The total number of possible solvent pairs disclosed in Tietze, Gordon, and Fessenden is greater than 135. *See* TX 0080 (Tietze); TX 0082 (Gordon); TX 0069x12 (Fessenden). Moreover, crystallization from solution also requires selection of temperatures or pH conditions, as well as the ratios to be used of the two solvents. *See* Trial Tr. (Genck Cross) 819:9-821:5; cf. *id.* (Atwood Direct) 936:10-937:11. In light of Dr. Genck's acknowledgement that one would not know which particular solvents would work without actually trying them, the hundreds if not thousands of possibilities facing one skilled in the art prior to Takeda's invention demonstrate the unpredictable nature of the invention.

239. Moreover, as Dr. Atwood explained, "[t]hese references are generally focused on doing rather simple crystallizations; not difficult ones," and thus would not lead one of skill in the art to have a reasonable expectation of crystallizing dexlansoprazole, especially in light of Larsson's unsuccessful attempt at evaporation from acetonitrile. *Id.* at 964:22-965:6.

240. Dr. Atwood's opinion is borne out by his own experience. Dr. Atwood's level of skill is far greater than that of one of ordinary skill in the art, as he has performed approximately 10,000 crystallizations over a 50-year career as a chemist. *See id.* (Atwood Redirect) 1062:6-15. Nonetheless, Dr. Atwood testified that he has been unable to crystallize complex molecules, not dissimilar from dexlansoprazole, 20 to 25 percent of the time. *See id.* (Atwood Direct) 941:12-18

(noting that when approaching a complex molecule that had not previously been crystallized, he "would not have an expectation that [he] would be successful"); *see also id.* (Genck Cross) 796:21-24 ("[s]ometimes [] compounds cannot generate a crystal form.").

241. In addition, as discussed above, Dr. Kamiyama, one of the inventors of the '282 Patent, in fact attempted "textbook methods" of crystallization, using such solvents as ethanol with hexane, ethyl acetate with hexane, THF, and methanol, but those methods failed to produce a crystal. *See* Trial Tr. (Kamiyama Direct) 88:11-23, 110:16-111:5. He was successful in obtaining the original crystal of dexlansoprazole by dissolving amorphous solid dexlansoprazole in acetonitrile, then evaporating at room temperature in a nitrogen stream, and adding diethyl ether, a technique not disclosed in any of the prior art cited by Defendants or Dr. Genck.

242. Further, as discussed above, Dr. Kamiyama used a crystal seed of the anhydrous crystal of dexlansoprazole from Example 1 of the '058 Patent to encourage crystallization of the sesquihydrate crystals disclosed in Example 3 and Step 2 of Example 2 of the '058 Patent. However, a technique that employs a crystal seed presupposes the existence of a suitable crystal for use in seeding. Here, the inventors necessarily had to obtain the original dexlansoprazole crystal without benefit of any pre-existing crystals to use as a seed. Indeed, as discussed above, Dr. Genck admitted that there were no dexlansoprazole seed crystals available before the first crystallization of dexlansoprazole disclosed in the'058 Patent. *See* Trial Tr. (Genck Cross) 808:14-18. The fact that crystallization sometimes requires the use of a crystal seed to be performed successfully is further indicative of the unpredictable and uncertain nature of crystallization.

243. Although Reference Example 4 did not use seed crystals, the crystallization process described in that Example to obtain the anhydrous crystal is extremely involved, involving five different solvents and four separate crystallization steps, and would not have been an obvious method for crystallizing dexlansoprazole at the time of the Takeda invention.

244. Accordingly, the Court finds that whether a given solvent or solvent combination would lead to the crystallization of dexlansoprazole, or whether dexlansoprazole could be crystallized at all, was unpredictable and not something as to which one ordinarily skilled in the art would have

had a reasonable expectation of success at the time of Takeda's invention. Defendants' reliance on previous disclosures of solvents used for the crystallization of other compounds, including commonly used solvents, as evidence of a reasonable expectation of success in crystallizing dexlansoprazole constitutes the use of impermissible hindsight, since one of ordinary skill in the art would know or expect that crystallization of dexlansoprazole using acetonitrile and diethyl ether as well as the other solvents disclosed in the examples of the '058 Patent would be successful only with the benefit of the patent's own disclosure.

245. The prior art disclosing crystallization of other PPIs, namely, Kato, Nohara, Kohl, and Bohlin, does not change the Court's conclusion that a person of ordinary skill in the art would not have had a reasonable expectation of success at the time of the invention.

246. Kato illustrates that entirely different types of crystalline compounds are obtained depending on which crystallization methods are used. The surprising and unexpected nature of Kato's invention of the method of producing the anhydrous crystal resulted in his obtaining a patent even though crystalline lansoprazole was known at the time of his invention. This is consistent with Dr. Atwood's testimony that the outcome disclosed in Kato would not have been predicted and that Kato supported his opinion concerning the unpredictability of crystallization. *See* Trial Tr. (Atwood Direct) 971:11-16.

247. A comparison of the results obtained for dexlansoprazole described in the '058 Patent with the disclosure in Kato with respect to racemic lansoprazole also supports this conclusion, and demonstrates the unpredictable nature of crystallization, even between racemates and enantiomers of the same compound. As discussed above, Kato discloses the synthesis of racemic lansoprazole in monoethanolate monohydrate crystalline form when it is crystallized from ethanol and water. *See, e.g.,* TX 0069x32, at TX 0069x32-0003, col.1, ll.26-40, 47-57; TX 0069x32-0007, col.9, l.46 to col.10, l.4 (Reference Example 6); *see also* Trial Tr. (Atwood Direct) 970:5-13. However, when the inventors of the '058 Patent attempted to crystallize dexlansoprazole using ethanol and water as the solvent, they were unable to obtain any crystals until they added a seed crystal. *See* Trial Tr. (Atwood Direct) 971:4-10; *id.* (Kamiyama Direct) 97:3-25. Dr. Kamiyama's laboratory notebook states that an oily phase precipitated as a result of the attempt to crystallize dexlansoprazole using

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ethanol and water as the solvent without addition of a seed crystal. *See* TX 0502 and TX 0502A (Kamiyama Notebook) at TX 0502A-0009. Moreover, when the inventors of the '058 Patent used an anhydrous seed crystal in their crystallization of dexlansoprazole with ethanol and water, the result was a sesquihydrate crystal, see TX 0001 ('058 Patent) at TX 0001-0007, col.12, l.11-14 (Example 3); TX 0502A (Kamiyama Notebook) at TX 0502A-0009; Trial Tr. (Atwood Direct) 970:19-971:10; *id.* (Kamiyama Direct) 96:14-100:15. Thus, they obtained neither the monoethanolate monohydrate crystal disclosed in Kato using ethanol and water for racemic lansoprazole, nor the anhydrous crystal taught by Kato when the monoethanolate monohydrate crystal was suspended and stirred in water. As Dr. Kamiyama testified, no ethanol remained in the dexlansoprazole sesquihydrate crystal he obtained using ethanol and water as solvents. Trial Tr. (Kamiyama Direct) 100:7-15. Moreover, although Dr. Kamiyama used a seed crystal of anhydrous crystal, he unexpectedly obtained a sesquihydrate crystal from his crystallization of dexlansoprazole using ethanol and water. *See. id.* (Kamiyama Direct) 99:25-100:4 (indicating that Dr. Kamiyama expected to get an anhydrous crystal from this experiment).

248. Nohara also would not have engendered a reasonable expectation of success as to the crystallization of dexlansoprazole. As mentioned above, Dr. Atwood testified that the fact that racemic lansoprazole could be crystallized did not suggest that the R-enantiomer of lansoprazole could also be crystallized. *See* Trial Tr. (Atwood Direct) 967:11-25. Dr. Atwood explained:

> Racemic lansoprazole is a different entity from dexlansoprazole. Racemic omeprazole is a different entity from S-omeprazole. The process of crystallizing a racemate is generally relatively straightforward. A process of crystallizing an optically pure enantiomer is much more difficult. They're the same types of molecules, but they crystallize differently. They have to crystallize differently. And this means that they behave more like two separate entities.

Id. 967:25-968:9 (emphasis added); *see also id.* 967:11-969:12.

249. Dr. Atwood testified that racemic compounds crystallize in what is called a "centric space group" whereas chirally pure enantiomers have to crystallize in one of the sixty-six acentric space groups. *Id.* (Atwood Direct) 968:10-16, 969:4-12. These represent different ways of packing the molecules in the crystals. *See id.* The racemic compound, containing molecules with both left- and

right-handedness, can more easily pack together in a crystalline structure. *See id.*

250. More crystalline structures thus are available for racemic compounds than for enantiomeric compounds. *See* TX 0084 (Datta & Grant) at TX 0084-0004 ("[T]he overall crystal structure of an enantiomer must be dissymmetric. Enantiomers can therefore crystallize in only 66 of the 230 space groups. . . . Racemic compounds, on the other hand, can crystallize in any of the 164 achiral space groups."); *see also* Trial Tr. (Atwood Direct) 969:4-12 ("[A]n optically pure enantiomer cannot crystallize in one of the centric space groups. It must crystalize in one of the 66 acentric space groups."). These differences in crystal structure mean that racemic crystals and the related enantiomeric crystals likely will crystallize under different conditions and have different physical properties. *Cf.* Trial Tr. (Atwood Direct) 967:25-968:9 (indicating that enantiomers and racemic compounds "crystallize differently" and "behave more like two separate entities").

251. Dr. Genck admitted that a racemic compound "could very well be packed more densely" than an enantiomer, *id.* (Genck Cross) 849:10-17, and that "given the difference in the crystal structure of a racemic mixture from an enantiomer, the fact that the racemic mixture might crystallize wouldn't necessarily mean that the enantiomer can also crystallize . . . ." *Id.* 848:25-849:5.

252. Dr. Genck's view that a person of ordinary skill would reasonably expect that dexlansoprazole could be crystallized based on Kohl's disclosure of the crystallization of an enantiomer of pantoprazole is similarly unpersuasive. *See* Trial Tr. (Genck Cross) 733:25-734:25, 761:11-763:15. Dr. Genck noted that Kohl lists several compounds that might be obtained using the disclosed method, including dexlansoprazole. *See* TX 0086 (Kohl) at TX 0086-0006; Trial Tr. (Genck Direct) 762:14-763:14. However, Kohl provides no working examples with dexlansoprazole, or even racemic lansoprazole. *See* TX 0086 (Kohl). Kohl merely incudes a list of compounds as "[p]articularly preferred compounds that can be prepared with the method according to the invention," without mentioning whether they would form crystals or even solids. TX 0086 (Kohl) at TX 0086-0006. Given that the list includes the (+)-enantiomer of omeprazole, which Kohl was only able to obtain in amorphous solid form, Kohl would not suggest to one skilled in the art that dexlansoprazole could be expected to be crystallized.

253. Although Dr. Genck testified that the invention described in Kohl resulted in a crystal, Trial Tr. (Genck Direct) 763:14-15, as noted above, and as Dr. Genck acknowledged, Kohl discloses successful crystallization of one benzimidazole enantiomer, (+) pantoprazole, and unsuccessful crystallization of another, (R+) omeprazole. *See id.* (Genck Cross) 856:18-20. Dr. Genck did not provide any explanation as to why one skilled in the art would find Kohl's teaching with regard to pantoprazole to be more relevant than its teaching regarding omeprazole. Thus, although Kohl might suggest that it could be possible to crystallize dexlansoprazole, it does not indicate that one would reasonably expect to be able to do so. Accordingly, the Court finds that Kohl demonstrates the unpredictability of crystallization of related benzimidazole compounds and supports the view that one of ordinary skill in the art would not have a reasonable expectation of success in crystallizing dexlansoprazole based on its disclosure. *See id.* (Atwood Direct) 965:17-21.

254. Bohlin also would not have given rise to a reasonable expectation of success. The starting material for the experiments disclosed in Bohlin was an S-omeprazole salt. Neither Dr. Genck nor Defendants have identified any prior art disclosing a dexlansoprazole salt prior to the '058 Patent. Because Bohlin does not teach crystallization starting from a neutral S-omeprazole compound, one skilled in the art would not consider its teachings to disclose how to make a neutral crystalline form of dexlansoprazole.

255. At trial, Dr. Genck pointed to Bohlin as a reference disclosing crystallization of a related compound, *see id.* (Genck Direct) 763:25-764:8, to support his opinion that crystallization of one compound provides one skilled in the art with a reasonable expectation of success in crystallizing another compound. *See id.* at 733:25-734:25. As reflected in the references cited above, however, including Larsson (which discloses crystals of enantiomers of benzimidazole compounds structurally related to omeprazole, including omeprazole salts, but only an oil of dexlansoprazole, *see* TX 0301 (Larsson II)) and Kohl (which discloses that amorphous or crystalline solids may result from the same crystallization procedures for related benzimidazole compounds), crystallization of enantiomers of related benzimidazole compounds is not predictive of whether a given enantiomer of a given benzimidazole compound can be crystallized. Thus, prior art

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crystallizations of enantiomers of other benzimidazole compounds would not have engendered a reasonable expectation of success prior to the '058 Patent that dexlansoprazole could be crystallized. Bohlin further confirms the unpredictability of crystallization, as the use of different methods with respect to isolation of S-omeprazole disclosed in Bohlin resulted in the formation of three different solid forms – amorphous solid, crystalline, and partially crystalline.

256. The foregoing facts corroborate Dr. Atwood's opinion that crystallization of dexlansoprazole, including crystallization to obtain the anhydrous crystal described in claim 1 of the '058 Patent, would have been highly unpredictable to one skilled in the art at the time of the Takeda invention.

f. Whether the Anhydrous Form of Dexlansoprazole Could have Been Predicted

257. The person of ordinary skill also would not have been able to predict, in view of the prior art, the anhydrous crystal with the characteristic d-spacings set forth in claim 1 of the '058 Patent because that crystal did not exist before Takeda made it and therefore, the particular d-spacings in claim 1 could not have been predicted. Dr. Genck admitted that the d-spacings in claim 1 could not have been predicted before Takeda's invention and that understanding that it might be possible to crystallize a compound would not tell a person of ordinary skill in the art the structure of the crystal until it was actually made. *See* Trial Tr. (Genck Cross) 799:20-25, 800:17-21, 801:25-802:6.

258. The anhydrous dexlansoprazole crystal has numerous properties that reflect its unique physical structure: a molecular weight of 369.36 g/mol, a melting point of 147.0-148.0 °C, a density of 1.452 g/cm^3, and a structure with the space group $P2_1$. *See* TX 0001-0006, col.10, l.53 to col.11, l.8, TX0001-0007, col.11, l.44; compare with the properties of the sesquihydrate dexlansoprazole crystal also disclosed in the '058 Patent, which has characteristic d-spacings of 3.00, 3.50, 4.49, 5.02, 5.65, 5.92, 6.61, 8.05, 8.87, 9.60, and 13.22 Angstroms and a melting point of 76.0-80.0 °C. *See* TX 0001-0007, col.12, ll.11-44; TX 0001-0008, col.14, ll.31-36. None of these properties would have been known or could have been predicted before Takeda's invention.

259. Dr. Genck testified that because the anhydrous crystal of claim 1 is the only known stable

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form of anhydrous dexlansoprazole resulting from crystallization from solvents, one necessarily would have expected to obtain this crystal. However, even if it became known *after* Takeda's invention that the crystal described in claim 1 was the most stable anhydrous crystal, that does not mean that this fact was known or knowable at the time of its invention. Nor would the skilled artisan have been able to predict which crystallization techniques would have resulted in the anhydrous crystal of dexlansoprazole.

3. Differences Between the Inventions of Claims 2 and 3 of the'276 Patent and the Prior Art

260. Handa and Impax also contend that claims 2 and 3 of the '276 Patent are obvious over the prior art.

261. As noted above, claim 2 of the '276 Patent requires a crystalline compound of dexlansoprazole or a salt thereof, and claim 3 requires a pharmaceutical composition comprised of the crystal according to claim 2 (or a salt thereof) and a pharmaceutically acceptable excipient, carrier, or diluent. *See* TX 0002 ('276 Patent) at TX 0002-0008, col.14, ll.59-67. The claims of the '276 patent thus cover different crystal forms of dexlansoprazole, including not only the anhydrous crystal, but also, for example, the sesquihydrate crystal disclosed and described in Example 3.

262. Dr. Genck testified that the basis for his opinion that the asserted claims of the '276 Patent are invalid is the same as his basis for his opinion that asserted claims of the '058 Patent are invalid. *See* Trial. Tr. (Genck Direct) 788:9-17. This is consistent with the fact that Dr. Genck did not offer any opinions that any crystals other than the anhydrous crystal described in claim 1 of the '058 Patent, such as the sesquihydrate crystal, or the methods of making such crystals, would have been obvious or predictable to one skilled in the art at the time of the Takeda invention. Instead, all of the prior art-based-arguments presented by Dr. Genck and advanced by defendants are equally applicable to the asserted claims of the '058 and '276 Patents. Therefore, the Court's findings above with respect to the validity of the '058 Patent apply equally to the validity of the '276 Patent.

263. The '276 Patent discloses several crystals other than the anhydrous crystal, including the

sesquihydrate crystal made in Example 3, and various intermediate crystal forms described in Reference Example 4. Prior to the work of the inventors of the '276 Patent, none of these crystals of dexlansoprazole had been synthesized. Moreover, it is undisputed that none of the chemical structure, d-spacings, or physical configuration of these crystal forms of dexlansoprazole could have been predicted prior to Takeda's invention, and could only be known after the crystals had been synthesized. *See* Trial Tr. (Atwood Direct) 975:8-16.

264. Moreover, as discussed above in the context of the '058 Patent, the disclosures of the prior art cited by Defendants and Dr. Genck would not have provided the person of ordinary skill with a reasonable expectation of success in synthesizing a crystal from the oil disclosed in Larsson. Rather, the person of ordinary skill would have understood, as set forth in Tietze and Vogel, that crystallization is an unpredictable and experimental art. *See, e.g.,* TX 0080 (Tietze) at TX 0080-0004; TX 0081 (Vogel) at TX 0081-0005.

265. Because these prior art references did not teach the person of ordinary skill how to crystallize dexlansoprazole, these references also did not teach the person of ordinary skill how to formulate a pharmaceutical composition comprised of a crystalline compound of dexlansoprazole, as required by claim 3 of the '276 Patent.

4. Differences Between the Inventions of Claims 6 and 7 of the '971 Patent and the Prior Art

266. Asserted claims 6 and 7 of the '971 Patent depend directly or indirectly from claim 5, which requires "[a] method of treating reflux esophagitis in a mammal in need thereof which comprises administering to said mammal an effective amount of a crystalline compound of [dexlansoprazole] or a salt thereof and a pharmaceutically acceptable excipient, carrier or diluent." TX 1054 ('971 Patent) at TX 1054-0009, claim 5.

267. Claim 7 further specifies that "said crystalline compound has an x-ray powder diffraction analysis pattern with characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom." *Id.* at claim 7.

268. Claim 6 is thus directed to a pharmaceutical composition of a crystalline compound of dexlansoprazole or a salt thereof, similar to claim 3 of the '276 Patent, while claim 7 specifies an

anhydrous crystalline compound of dexlansoprazole with the same d-spacings claimed in claim 3 of the '058 Patent.

269. Impax contends that claims 6 and 7 of the '971 Patent are obvious for the same reasons that the asserted claims of the '058 and '276 Patents are obvious.

270. The Court makes the same findings of fact in connection with claim 6 of the '971 Patent that it made above in connection with claim 3 of the '276 Patent. Similarly, the Court makes the same findings of fact in connection with claim 7 of the '971 Patent that it made above in connection with claim 3 of the '058 Patent.

271. In addition, as discussed above, the person of ordinary skill would not have been able to predict, in view of the prior art, the patented subject matter itself – namely, the anhydrous crystal with the characteristic d-spacings set forth in claim 7 of the '971 Patent. Moreover, Impax has presented no evidence that, prior to Takeda's invention, the skilled person would have known of the existence of or expected to make a polymorph having the structural characteristics of this crystal.

E. Findings of Fact Relating to Plaintiffs' Standing to Assert the '282 Patent

272. TWi contends Plaintiffs TPNA, Takeda LLC, and TPA (collectively, "the Takeda U.S. entities") do not have standing to sue for infringement of the '282 Patent because: 1) a provision in the relevant license agreement requiring TPNA to purchase its dexlansoprazole drug product from TPC negates the grant of exclusive rights; and 2) the grant of an exclusive license in the field of acid-related disorders was insufficient because the '282 Patent covers a compound and not a field of use.

273. The facts relevant to this standing issue are not in dispute and are set forth in a stipulation served on TWi by Takeda on August 2, 2012. *See* TX 0244 (Stipulation Regarding Interests Held by Plaintiffs in the Patents-in-Suit) ("Stipulation").

274. As set forth in the Stipulation, Plaintiff TPC is the owner of record and assignee of the asserted patents, including the '282 Patent. *See* TX 0244 at ¶ 1. In 2004, TPC (formerly known as Takeda Chemical Industries, Ltd.) and TPNA (successor-in-interest to TAP Pharmaceutical Products ("TAP")) signed a license agreement ("License Agreement") in which TPC granted an

exclusive license under the patents-in-suit to sell dexlansoprazole drug products in the United States for the treatment of acid related disorders. *See* TX 0221 (License Agreement); TX 0244 at ¶¶ 1, 24-25.

275. The rights of the other U.S. entities – TPA and Takeda LLC – are detailed in Trial Exhibit 244 and are derivative of the rights granted by TPC to TAP in the License Agreement. *See* TX 0244-0002- to -0007(Stipulation Regarding Interests Held by Plaintiffs in the Patents-in-Suit) at ¶¶ 5-30. TWi's standing challenge is based only on the License Agreement between TPC and TAP; TWi does not dispute that whatever rights were conveyed to TAP (and therefore to its successor-in-interest, TPNA) under the License Agreement have also been conveyed to the other U.S. entities.

276. Section 2.1(a) of the License Agreement describes the license granted by TPC:

> Licensor hereby grants to Licensee an Exclusive License in the Field under the Patent Rights and Technical Information (i) to offer for sale and sell the Product in the Territory; (ii) to offer for sale and sell the Finished Compound to Repackagers in the Territory and (iii) to sell the Product to Sub-licensees for their offer for sale and sales in Canada and Puerto Rico under Section 2.3. For such purposes, Licensor also hereby grants to Licensee the right to import the Finished Compound from Licensor or Licensor's Designated Manufacturer into the Territory and package or have packaged the Finished Compound in the Territory, and to package and have packaged the Finished Compound into the Product outside the Territory and to import such Product into the Territory.

TX 0221-0004.

277. "Field" is defined as "the cure, mitigation, control, treatment or prevention of any acid related disorder." TX 0221-0002.

278. "Product" is defined in the License Agreement as "the Finished Compound packaged for commercial sale by itself or as a component of a Bundled Product." TX0221-0004.

279. "Finished Compound" is defined as "the Compound in a dosage form that is suitable for human use, such as a tablet or capsule, but which has not yet been placed into packaging for commercial sale." TX 0221-0002.

280. "Compound" is defined as "the compound that is identified by Licensor as TAK-390 [dexlansoprazole] and which has the chemical name and structure described in Exhibit A hereto,

including its various salts, crystalline forms, hydrates and free forms." TX0221-0001.

281. "Territory" means "(i) the United States and its territories and possessions, including Puerto Rico, and (ii) Canada." TX 0221-0004, Section 1.22.

282. The term "Exclusive License" is defined in the License Agreement as "a license under which the Licensee's rights are sole and exclusive and operate to exclude all others, including the Licensor [TPC]." TX 0221-0002, Section 1.7.

283. The term "Patent Rights" is defined as follows:

> "Patent Rights" means any United States or Canadian patents or patent applications currently existing or hereafter filed or acquired by Licensor, or licensed to Licensor with the right to sublicense to Licensee, which relates to the Compound, Finished Compound, and/or Product, including any addition, division, continuation, continuation-in-part, substitution, extension, renewal, reexamination or reissue of any of the aforementioned patent applications or patents. Patent Rights shall include but not be limited to the patents and patent applications listed in Exhibit B.

TX 0221-0003, Section 1.17; *see also* TX 0221-0018 TX 0221-0019 (Exhibit B). Exhibit B specifically lists U.S. Patent Application No. 09/674,624, the application to which the '282 Patent claims priority. TX 1055-0001 ('282 Patent).

284. Section 2.1(b) of the License Agreement states, "Licensee shall not import into the Territory or offer for sale or sell in the Territory the Compound or Finished Compound that is not manufactured by Licensor or Licensor's Designated Manufacture and shall prohibit Sub-licensees from doing so." *See* TX 0221-0004. Pursuant to Section 2.1(b), TPNA may not import or sell dexlansoprazole drug product that is not manufactured by TPC.

285. Although Section 2.1(b) limits the product that TPNA itself may import and sell under the License Agreement, it does not limit TPNA's right to exclude others from importing or selling dexlansoprazole drug products within the United States under Section 2.1(a). Other provisions in the License Agreement support this interpretation of Section 2.1(a) and (b). For example, Section 10.1 contemplates TPNA joining TPC as a plaintiff in patent infringement lawsuits. *See* TX 0221-0011 ("Licensee shall join as a plaintiff if required to do so by law or by Licensor or may join as a plaintiff if Licensee deems it necessary."). Other provisions contemplate that TPNA will file a New Drug Application with the FDA and list TPC's patents in the Orange Book. *See* TX 0221-

0007 (Section 5.2) and -0010 (Section 8.3).

286. Viewed as a whole, the License Agreement between TPC and TPNA grants TPNA exclusive rights to the patents covering dexlansoprazole so that TPNA may sell TPC's drug products in the United States and exclude others from selling generic dexlansoprazole products covered under the patents listed in Exhibit B to the License Agreement. The requirement that TPNA purchase its dexlansoprazole drug products from TPC does not negate the grant of exclusive rights in the license agreement.

287. In addition, because only TPNA has the exclusive right under the '282 Patent to import and sell dexlansoprazole drug products in the United States for the treatment of acid reflux disease, *see* TX 0221-0004 (Section 2.1), TPNA can block TWi from obtaining a license from TPC to practice the '282 Patent in connection with its ANDA products.

F. Findings of Fact Relating to Declaratory Judgment Jurisdiction

288. Count VII of Takeda's First Amended Complaint against TWi seeks a declaratory judgment that the future "commercial manufacture, use, sale or offer for sale" of TWi's proposed ANDA products "will constitute infringement" of the '282 Patent pursuant to 35 U.S.C. §§ 271(a), (b), and/or (c). First Amended Complaint [Case No. 3:11-cv-1609, D.N. 19] at ¶ 61.

289. TWi's Abbreviated New Drug Application No. 202-666 was filed on December 1, 2010, was accepted for filing by the FDA on February 7, 2011, and remains pending before the FDA. TX 1371 (Additional Stipulated Facts for Trial) at TX 1371-0002 ¶ 1.

G. Findings of Fact Related to the Validity of the '282 Patent

290. Handa and TWi contend prior art anticipates or renders obvious asserted claims 1 and 2 of the '282 Patent. *See* Trial Tr. (Handa's Opening Statement) 33:25-34:4.

291. Handa and TWi also contend the asserted claims of the '282 Patent are invalid for lack of adequate written description because a person of ordinary skill would not have understood the inventors to have had possession of an amorphous compound of dexlansoprazole or the preparation of a "salt thereof." *Id.* (Handa's Opening Statement) at 38:14-39:13 (stating that Handa's written description challenge is based on alleged absence of adequate disclosure of amorphous compound of dexlansoprazole in '282 Patent); Handa, Par and TWi's Post-Trial Brief

at 58-59 (arguing that claims 1 and 2 of '282 Patent are invalid because the specification does not adequately disclose amorphous *salts* of dexlansoprazole).

292. At trial, Defendants' expert Dr. Robin Rogers testified regarding his opinion that the asserted claims of the '282 Patent are invalid. In his opinion, Dr. Rogers relied in part on the experiments performed under the direction of Dr. Edmund Elder at the University of Wisconsin.

293. Takeda's expert Dr. Jerry Atwood testified regarding the validity of the asserted claims of the '282 Patent.

1. Anticipation

a. Handa's and TWi's Contention that Barberich II Anticipates an Amorphous Compound of Dexlansoprazole

294. Handa and TWi contend that claims 1 and 2 of the '282 Patent are anticipated by Barberich II.

295. The Barberich II reference discloses solid pharmaceutical compositions of dexlansoprazole. *See, e.g.*, TX 0078-0005 (Barberich II) at [0035] (teaching that "[c]ompressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules").

296. Despite Barberich's purported disclosure of solid pharmaceutical compositions of dexlansoprazole, Defendants have not established by clear and convincing evidence that the person of ordinary skill would have been able to make the amorphous solid of dexlansoprazole described by Barberich without undue experimentation. Rather, the preponderance of the evidence establishes that undue experimentation would have been required to make the amorphous solid of dexlansoprazole described in Barberich.

i. The Amount of Direction or Guidance Provided by the Specification

297. The Barberich specification provides no direction or guidance as to how to convert the oil in Larsson into a solid. *See* Trial Tr. (Rogers Cross) 617:18-23; 666:17-667:13 (testifying that "[t]here's no written statement" in Barberich II regarding how to change the oily form of dexlansoprazole disclosed by Larsson and Von Unge into a solid).

298. Instead, Barberich incorporates by reference the synthesis methods disclosed in the Larsson I (WO 96/02535) and Von Unge I (WO 97/02661) references, as stated above.

299. As discussed above, Larsson and Von Unge disclose only the oily form of dexlansoprazole. *See* Trial Tr. (Elder Direct) 383:19-21; *id.* (Elder Cross) 399:11-13 (testifying that Larsson reported obtaining an oil of dexlansoprazole); Trial Tr. (Rogers Cross) 666:3-16 (testifying that Larsson and Von Unge disclose an oil of dexlansoprazole); *see* also TX 0301-0010 (Larsson II) at col.18, ll.32-35 ("Repeating this procedure a couple of times afforded 0.31 g (14%) of the desired compound *as an oil* with an optical purity of 99.6% e.e.") (emphasis added); TX 0302-0006 (Von Unge II) at col.9, ll.29-31 ("Repeating this procedure a couple of times afforded 0.31 g of the desired compound *as an oil* with an optical purity of 99.6% e.e.") (emphasis added).

300. The lack of direction or guidance in Barberich regarding how to convert the oil in Larsson into a solid weighs against a finding that one skilled in the art could make the solid amorphous compound of dexlansoprazole described by Barberich without undue experimentation.

ii. The Absence of Working Examples Set Forth in the Specification

301. The Barberich specification does not contain any working examples regarding how to synthesize solid dexlansoprazole. *See* Trial Tr. (Atwood Direct) 900:18-901:3. There is no evidence that Barberich ever actually obtained the solid. *See id.*; *see also id.* (Rogers Cross) 617:18-23; 666:17-667:13 (testifying that "[t]here's no written statement" in Barberich II regarding how to change the oily form of dexlansoprazole disclosed by Larsson and Von Unge into a solid).

302. The absence of any working examples of how to convert the oil in Larsson into a solid weighs against a finding that one skilled in the art could make the solid amorphous compound of dexlansoprazole described by Barberich without undue experimentation.

iii. The Nature of the Invention and the Relative Skill of a Person of Ordinary Skill in the Art

303. The invention of Barberich II is a pharmaceutical formulation of dexlansoprazole. *See* Trial Tr. (Atwood Direct) 901:8-12; *see* also TX 0078-0001 (Barberich II) ¶ [0002] ("This

invention relates to compositions of matter containing lansoprazole. The invention also relates to methods of treating and preventing ulcers, treating other conditions related to gastric hypersecretion, and treating psoriasis.").

304. The level of skill of the person of ordinary skill in the art of the Barberich invention is very similar to the level of skill of a person of ordinary skill in the art of the Takeda patents, discussed above, but the focus of such a person would be on formulation because Barberich is a formulation patent. *See* Trial Tr. (Atwood Direct) 901:13-902:13.

iv. The State of the Prior Art

305. As discussed above, the Larsson and Von Unge references are the closest prior art references and are incorporated into Barberich. Neither Larsson nor Von Unge discloses the synthesis of a solid form of dexlansoprazole. *See* Trial Tr. (Atwood Direct) 902:21-903:13 ("[d]exlansoprazole was known only as an oil"); *id.* (Rogers Cross) 617:18-23, 666:17-667:13 (testifying that "[t]here's no written statement" in Barberich II regarding how to change the oily form of dexlansoprazole disclosed by Larsson and Von Unge into a solid).

v. Predictability or Unpredictability of the Art

306. The art of pharmaceutical formulation, as described in the Barberich reference, was relatively predictable at Barberich's priority date. *See* Trial Tr. (Atwood Direct) 903:20-25.

307. On the other hand, the synthesis of solid dexlansoprazole, which falls within the field of organic chemistry, was unpredictable. Organic chemistry is an experimental science, meaning that one cannot predict the outcome of an experiment without actually carrying out the experiment (such as a crystallization or synthesis) in the laboratory. *See* Trial Tr. (Atwood Direct) 903:20-905:5 ("one has to go into the laboratory, one has to carry out the reactions, carry out the crystallizations, carry out the solidification, and see what one gets. It's unpredictable, the experimental aspect of chemistry"); cf. TX 0081-0005 (Vogel) (listing generalizations to assist in the selection of a crystallization solvent, but noting that "numerous exceptions are known").

308. The disclosure of Larsson supports Dr. Atwood's opinion that at the time of the invention, the field of synthetic chemistry was unpredictable. Larsson was able to obtain enantiomeric solids of omeprazole and compounds (Ib), (Ic), (Ie), and (Ih), but unable to obtain solid forms of

lansoprazole – even though Larsson performed the final purification step with acetonitrile at least three times in the case of dexlansoprazole. Larsson was likewise unable to obtain solid forms of the enantiomers of the related chemical compounds pariprazole and leminoprazole.

309. Although Larsson reflects the state of the art in 1995 and Barberich II reflects the state of the art in 1998, the parties agree that the state of the art with respect to techniques for obtaining amorphous solids did not change between 1995 and 1998. Trial Tr. (Rogers Cross) 632: 16-22.

310. The unpredictability of the art of organic chemistry weighs against a finding that one skilled in the art could make the solid amorphous compound of dexlansoprazole described by Barberich without undue experimentation.

vi. The Breadth of the Claim

311. Barberich states that its pharmaceutical formulations can take either solid or liquid form. *See* TX 0078-0004 (Barberich II) at [0032] ("The compositions of the present invention include suspensions, solutions, elixirs, or solid dosage forms."); *see also id.* at [0029], [0034]. The claims of the Barberich reference also encompass both solid and liquid pharmaceutical formulations of dexlansoprazole. *See id.* at p. 5 (Claims). Thus, despite Barberich's failure to disclose the synthesis of solid dexlansoprazole, the person of ordinary skill could have used the oil of dexlansoprazole disclosed in Larsson to make a liquid formulation of dexlansoprazole that would have fallen within the scope of the Barberich claims. *See* TX 0078-0004 (Barberich II) at [0034] ("Pharmaceutical compositions of the present invention suitable for oral administration may be presented as . . . an oil-in-water emulsion, or a water-in-oil liquid emulsion."); Trial Tr. (Rogers Cross) 618:22-619:6 ("I think if dexlansoprazole was an oil, then you could incorporate that into an emulsion, along with whatever solvent was with it."); Trial Tr. (Atwood Direct) 905:6-24.

vii. The Quantity of Experimentation Needed and the Experiments at the University of Wisconsin

312. The only evidence in the record of anyone attempting to make a solid form of dexlansoprazole by following the teachings of Example 22 of Larsson is the work carried out under the direction of Dr. Elder at the University of Wisconsin ("UW") in 2012, fourteen years after Barberich was filed. *See* Trial Tr. (Elder Direct) 362:18-23 (testifying that he reviewed and

approved all of the work that Dr. Feltenberger or the UW lab performed); *id.* (Elder cross) 387:8-389:8 (testifying that the UW experiments were carried out under his direction); *id.* (Rogers Direct) 626:24-627:4 (testifying that Dr. Elder planned, designed, and oversaw the UW lab's work). The UW lab attempted to repeat Example 22 of Larsson in two separate experiments, referred to as ED-12 and ED-13. *See* TX 0733x03 (UW Report).

313. Dr. Elder received a bachelor's degree in pharmacy in 1985 and a Ph.D. in pharmaceutical sciences in 1989 from the Medical University of South Carolina. *See* TX 0733x01-0002 (Dr. Elder's curriculum vitae). He then spent 16 years as a formulation scientist in the pharmaceutical industry. *See* Trial Tr. (Elder Direct) 353:9-12. Since 2007, he has been the director of the Zeeh Pharmaceutical Experiment Station at UW, which provides drug development services and educational programming to researchers in academia and the pharmaceutical industry. *See* TX0733x01-0002 (Dr. Elder's curriculum vitae); Trial Tr. (Elder Cross) 386:9-23.

314. During his career, Dr. Elder has gained "extensive experience characterizing pharmaceutical materials, including drugs, and formulating and testing pharmaceutical products." Trial Tr. (Elder Cross) 386:13-16. Dr. Elder thus possesses greater than ordinary skill in the art of the Barberich patent. *See* Trial Tr. (Rogers Cross) 627:1-14 (testifying that Dr. Elder's level of skill is "a bit higher" than the threshold level of skill for one of ordinary skill); Trial Tr. (Elder Cross) 386:24-387:7 (testifying that the person of ordinary skill in the art of the Larsson patent "would have been exposed to asymmetric-oxidation-type reactions, but may not have actually conducted them in a laboratory themselves.").

a. Dr. Elder's First Attempt to Replicate Example 22 of Larsson

315. Dr. Elder's first attempt to replicate Example 22 of Larsson was a "failure." Trial Tr. (Atwood Direct) 908:9-12; *see also id.* (Rogers Cross) 628:7-19 (testifying that Dr. Elder's first attempt did not "get the result that Larsson got"); *id.* (Rogers Cross) 658:24-660:18. Dr. Rogers also testified that he is not relying on Dr. Elder's first attempt to replicate Example 22 of Larsson for his opinion that Barberich anticipates the '282 Patent. *See id.* (Rogers Cross) 656:2-8.

316. In this first attempt, referred to in the UW Report as "ED-12," the UW lab opted for a "literal interpretation of Larsson." Trial Tr. (Rogers Direct) 513:3-10; *id.* (Elder Cross) 389:14-17

(testifying that he "opted for as strict an interpretation of the Larsson procedure as possible"); TX 0733x03-0004 (UW Report) ("[F]or our first reaction we opted for as strict of interpretation of the Larsson procedure as possible."). Each reagent, including the oxidant, 1.1 mL of cumene hydroperoxide ("CHP"), was added "in one portion," or all at once. Trial Tr. (Elder Cross) 389:18-21; TX 0733x03-0004 (UW Report).

317. Instead of obtaining a residue with an enantiomeric excess ("e.e.") of 46% as did Larsson after the asymmetric oxidation and extraction, evaporation, and flash chromatography steps, UW's first attempt resulted in a solid of "nearly racemic" lansoprazole, with only a "slight preference" (6% e.e.) for dexlansoprazole. TX 0733x03-0004-5 and -0008 (UW Report). Dr. Elder testified that "an EE of 6 percent was not as good as [he] would have liked." Trial Tr. (Elder Cross) 391:8-392:5. Moreover, it would have been difficult – and no attempt was made – to isolate the excess dexlansoprazole from this mixture. *See* Trial Tr. (Rogers Cross) 658:16-19 ("[I]t would have been difficult to isolate that 6 percent."); *id.* (Elder Direct) 373:5-13 ("we ended up with 1.6 grams of material, which would represent dexlansoprazole and the racemate. So we would have to isolate the dexlansoprazole portion of that. Since it was only a 6 percent enantiomeric excess, we would have a very small yield if we were to go through and do additional isolation and, so, we decided not to do that. There wouldn't have been enough to further characterize the material"); *id.* (Atwood Direct) 908:3-8.

318. In addition, there is no evidence regarding the chemical purity of the "nearly racemic" solid obtained by the UW lab in this first attempt to replicate Example 22. *See* Trial Tr. (Rogers Cross) 657:14-658:11. Therefore, the Court concludes that the results of the first attempt by the UW lab to duplicate Example 22 of Larsson do not provide clear and convincing evidence that a person of ordinary skill in the art would have been able to create an amorphous compound of dexlansoprazole based on Larsson.

b. Dr. Elder's Second Attempt and the Dropwise Addition of CHP

319. In UW's second attempt to replicate Example 22 of Larsson, referred to in the UW Report as "ED-13," the UW lab departed from the literal teachings of Example 22 by adding the oxidant CHP drop-by-drop over a period of 60 minutes via syringe pump – a procedure that is not

described in Example 22. *See* TX 0733x03-0005 and -0009 (UW Report); TX 0301-0010 (Larsson II) at Example 22, col.18, ll.17-18.

320. Dr. Elder testified that he and Dr. Feltenberger determined that two factors could greatly enhance the enantioselectivity of this reaction: slow addition of the oxidant (CHP) and lower reaction temperature. The person of ordinary skill would have understood that these techniques were interchangeable, because these techniques were simply alternate ways of controlling the temperature of the oxidation reaction. *See* Trial Tr. (Elder Cross) 392:16-393:21 (testifying that these two factors would have had the same effect on the rate of reaction and either one would have worked to improve the enantioselectivity of the oxidation reaction); *see also id.* (Rogers Direct) 515:12-20 ("[O]ne of skill in the art in this area would know that the addition of the CHP too fast can affect the enantiomeric selectivity, particularly by causing a rise in temperature. And they would know that you would need to add it slowly, or control the addition."); *id.* (Rogers Direct) 515:21-25, 633:14-19 ("Well, the art at the time had taught that if you add this too fast, it could raise the temperature, and it could lead to a lower enantiomeric excess or selectivity.").

321. Because these techniques were interchangeable, and Example 22 explicitly stated that the oxidation was performed at room temperature, Dr. Elder decided to improve the enantioselectivity of the reaction by slowing the addition of the oxidant using a syringe pump. Trial Tr. (Elder Cross) 392:16-393:21. Because both changes are ways of accomplishing the same purpose, Dr. Elder's modification was akin to lowering the temperature of the oxidation reaction.

322. Although Dr. Elder initially testified based on the UW Report (TX 0733x03-0009) that the CHP was added over a period of 30 minutes, he admitted that he could not explain the phrase "in 60 min. addition time" in Dr. Deng's laboratory notebook. TX 0733x05-0003 (Deng's notebook); *id.* (Elder Cross) 394:10-19. The Court rejects Dr. Rogers' testimony that the phrase "60 min." in the notebook is illegible, and credits the notebook entry that the addition of cumene hydroperoxide occurred over 60 minutes, with the color changing to yellow after 30 minutes. Trial Tr. (Rogers Cross) 630:9-632:7; *id.* (Atwood Direct) 909:6-12 (testifying that UW "made the change so as to

add this oxidizing agent over a period of 60 minutes rather than all at once").[5]

323. Nothing in Larsson would have suggested to the person of ordinary skill in the art that 1.1 milliliters of oxidant – about one fifth of a teaspoon, Trial Tr. (Rogers Cross) 629:15-22 – should have been added over 60 minutes. *See* Trial Tr. (Atwood Direct) 913:8-17; *id.* (Rogers Cross) 651:9-12 (testifying that he is "not aware of any example in Larsson where he indicates that the oxidant was added at room temperature over a 60-minute time period"). Although Dr. Rogers noted that a person of ordinary skill would have understood that the oxidant added in Larsson Example 11 would need to be added over time, that Example involved 3.3 kilograms of oxidant, which is a far greater amount than the amount added in Example 22. *See* Trial Tr. (Rogers Cross) 637:7-638:13; TX 0301-0008 (Larsson II) at Example 11, col.13, ll.64-66.

324. Dr. Rogers's testimony to the contrary was not credible. The prior art references relied upon by Dr. Rogers do not support his opinion that one skilled in the art would know to add the 1.1 milliliters of oxidant in Example 22 over a period of 60 (or even 30) minutes. *See* Trial Tr. (Rogers Cross) 639:17-647:17 (testimony regarding Trial Exhibits 146x23 (Zhao 1987), 146x18 (Zhao 1990), 146x16 (Diter 1994), 147 (Brunel1995), and 146x17 (Bolm and Bienwald 1995)). Dr. Rogers admitted that the sensitivity of the asymmetric oxidation reaction depends upon the particular compounds and catalysts and other reagents that are used. *See* Trial Tr. (Rogers Cross) 633:20-634:12. One of Dr. Rogers's prior art references involved different catalysts, and thus provided no guidance with regard to the enantioselectivity of an oxidation reaction using cumene hydroperoxide. *See, e.g.,* Trial Tr. (Rogers Cross) 646:25-647:17 (TX 0146x17 (Bolm and Bienwald 1995)). Other prior art references did not specify the rate of addition of the oxidant, *see, e.g.*, Trial Tr. (Rogers Cross) 640:17-23 (TX 0146x23 (Zhao 1987)); *id.* (Rogers Cross) 643:11-14 (TX 0146x16 (Diter 1994)); *id.* (Rogers Cross) 649:7-18 (Rogers Cross) (TX 0146x22 (Ramón 2006)). The mere mention of dropwise addition of an oxidant is not the same as, and does not provide support for, the extremely slow addition of less than a teaspoon of oxidant over an hour's time. Further, none of the references relied upon by Dr. Rogers involves the synthesis of

[5] Even if the CHP was added over a 30 minute period, as stated in the UW report, the Court's conclusions would be the same.

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dexlansoprazole. *See* Trial Tr. (Atwood Direct) 909:13-910:1; *id.* (Rogers Cross) 634:19-23 (admitting that the sensitivity of the oxidation reaction could depend on the compound that is being oxidized). Indeed, another reference around the time of the references on which Dr. Rogers relied specified the *rapid* addition of cumene hydroperoxide. *See also id.* (Rogers Cross) 644:15-23 (testifying that TX 0147 (Brunel 1995) specifies the "rapid addition" of cumene hydroperoxide).

325. Further, all of the oxidation experiments described in Dr. Rogers's prior art references were carried out at or below minus 15 degrees Celsius (about five degrees Fahrenheit), much lower than room temperature at which Example 22 was carried out. *Id.* (Atwood Direct) 910:13-911:3; *id.* (Rogers Cross) 638:14-639:16. The fact that the oxidation reactions described in these prior art references were carried out at low temperatures is significant because, as Dr. Rogers and Dr. Elder testified, low temperatures and the slow addition of the oxidant were part of the pre-Larsson teachings as to conditions that affected the enantioselectivity of the oxidation reaction. *See id.* (Elder Cross) 392:16-393:21; *id.* (Rogers Direct) 515:12-20; *id.* (Rogers Direct) 515:21-25 ("Well, the art at the time had taught that if you add this too fast, it could raise the temperature, and it could lead to a lower enantiomeric excess or selectivity.").

326. However, by the time of Larsson, Larsson itself would have provided the most up-to-date disclosure regarding how to add the oxidant in an asymmetric oxidation reaction for the person of ordinary skill attempting to replicate Example 22 in 1998 (the priority date of the Barberich reference) or 1999 (the priority date of the '282 Patent). *See* Trial Tr. (Atwood Direct) 911:4-14; cf. Trial Tr. (Rogers Cross) 635:15-637:6. Larsson taught away from the references cited by Dr. Rogers to the extent they taught the slow addition of the oxidant to control the temperature of the reaction.

327. The person of ordinary skill reviewing Larsson would not have concluded that the slow addition of oxidant was necessary because Larsson teaches, in contrast to the prior art, that, "[s]urprisingly, the process does not require a temperature below -20° C., as described by Kagan and co-worker as essential for good enantioselectivity." TX 0301-0005, col.8, ll.44-47; *see* Trial Tr. (Atwood Direct) 911:4-912:19; *id.* (Rogers Cross) 638:14-639:2, 651:3-8 ("[O]ne of

[Larsson's] big advances . . . was to be able to do this [oxidation reactions] at room temperature or above."); *id.* (Rogers Cross) 650:10-16 (testifying that the ability to perform oxidation reactions at room temperature "was one of the main things that Larsson was suggesting").

328. Because slowing down the rate of oxidant addition is an alternative to simply lowering the temperature of the reaction, the person of ordinary skill would conclude from this teaching in Larsson that neither a low temperature nor the dropwise addition of 1.1 milliliters of oxidant over 60 minutes should affect enantioselectivity, or be an appropriate departure from the specific teachings of Example 22. Trial Tr. (Atwood Direct) 911:4-913:7 ("One of ordinary skill would not have done that because the key reference . . . is the Larsson patent; and Larsson is showing in the patent that, unlike the prior art, it's possible to carry out these reactions at room temperature or slightly above. . .").

c. Other Departures from the Procedure in Example 22 of Larsson

329. Dr. Elder engaged in further experimentation beyond the disclosure in Example 22 of Larsson with respect to the solvents used for the extraction, evaporation, and flash chromatography steps. *See* Trial Tr. (Atwood Direct) 913:18-22 (confirming that the extraction, evaporation, and flash chromatography steps are sometimes referred to as "workup procedures"). Dr. Elder selected ethyl acetate for the extraction step. TX 0733x03-0009 (UW Report) ("the workup procedure employed extraction by ethyl acetate"). For the flash chromatography step, he chose to use a mixture of hexane and ethyl acetate in a gradient starting with a ratio of one part hexane to two parts ethyl acetate and ending with 100% ethyl acetate. *Id.* ("the workup procedure employed . . . silica gel flash column chromatography [gradient eluent: 1:2 hexane/EtOAc to 100% EtOAc]").

330. Although one skilled in the art at the time of Larsson would have had prior publications available to teach appropriate solvents for extraction or flash chromatography, the UW lab did not use the solvent combinations taught by the art. None of the references relied upon by Dr. Rogers to support the modifications to the protocol made by the UW lab describes a gradient elution method, nor does Larsson teach that method. *See* Trial Tr. (Atwood Direct) 914:25-915:15; *id.* (Elder Cross) 395:11-16 (discussing Larsson); *id.* (Elder Cross) 395:23-396:25 (admitting that the

Zhao reference (TX 0146x23) consulted by Dr. Elder during the UW experiments discloses different solvents than those he used and does not describe the use of a gradient column); *id.* (Rogers Cross) 652:18-653:1 (admitting that none of the prior art references on which Dr. Rogers relied discloses ethyl acetate and hexane or ethyl acetate and hexane in a gradient for flash chromatography).

331. The selection of the particular solvents and the ratios for the gradient would not have been a matter of routine experimentation for the person of ordinary skill implementing Example 22. *Id.* (Atwood Direct) 915:16-916:8. The purpose of the flash column chromatography step is to separate the different chemical entities present at the end of the oxidation reaction (namely, sulfides, sulfoxides, and sulfones). Considerable experimentation would be required to determine the solvent combination that would result in a good separation of these chemical entities. *Id.*

332. Dr. Elder also departed from the procedure set forth in Example 22 of Larsson by performing either five or six rounds of purification with acetonitrile instead of the three rounds described in Larsson. *See* Trial Tr. (Atwood Direct) 916:9-15; TX 0733x05-0003 (showing six acetonitrile steps: "first 50 mL[;] 2# 50 mL[;] 3# 30 mL[;] 5 mL[;] 5 mL[;] 5 mL"); *id.* (Elder Cross) 398:5-9 (testifying that"[t]here did seem to be an extra entry" in Dr. Deng's notebook for a sixth acetonitrile purification but that the UW report stating that the acetonitrile purification step was performed five times was correct). Moreover, the enantiomeric purity at the end of the third round, at 91.2% e.e., was significantly lower than the 99.6% e.e. disclosed in Larsson after three rounds of purification with acetonitrile. *See* TX 0733x03-0010 (UW Report); TX 0301-0010 (Larsson) at Example 22, col.18, ll.33-35; Trial Tr. (Atwood Direct) 920:6-921:5.

333. In fact, even after six rounds of purification with acetonitrile, the enantiomeric purity of 97.8% e.e. for the solid obtained by Dr. Elder was still less than the 99.6% e.e. for the oil obtained by Larsson. *See* Trial Tr. (Atwood Direct) 920:21-921:5.

d. Dr. Elder did Not Obtain an Oil of Dexlansoprazole

334. Through these modifications and choices, Dr. Elder obtained a solid, not an oil, immediately after the workup procedure. *See* Trial Tr. (Atwood Direct) 921:25-922:6 (testifying that the various departures from Example 22 made by UW "certainly led to a different result

because the Wisconsin group got a solid and Larsson got an oil").

335. In fact, Dr. Elder never obtained an oil of dexlansoprazole. *See* Trial Tr. (Rogers Cross) 654:5-18 (testifying that Dr. Elder obtained a solid before the acetonitrile step and never obtained an oil); *id.* (Elder Direct) 399:14-23 (testifying that the UW lab did not obtain an oil). Because Dr. Elder never obtained an oil of dexlansoprazole, UW's experiments are not a faithful re-working of Larsson Example 22 but, rather, a departure from Larsson and, thus, fail to establish that the oil obtained by Larsson could have been evaporated to dryness to obtain a solid. *Id.* (Atwood Direct) 922:7-13; *id.* (Rogers Cross) 654:16-656:1 (admitting that "the University of Wisconsin never converted an oil into a solid," and that the UW experiment "is not an instance of someone obtaining an oil, and simply doing more drying to remove the solvent").

336. In addition, the "residue" obtained by Larsson following the workup procedures had a very high chemical purity of 99.9%. *See* TX 0301-0010 (Larsson II) at Example 22, col.18, ll.26-29. In contrast, the chemical purity of the "light, brown solid" obtained by Dr. Elder following the workup procedures is unknown and unreported. Trial Tr. (Elder Cross) 400:14-17 ("We [did] not do an achiral HPLC to determine that."); *id.* (Atwood Direct) 918:15-919:5; TX0733x03-0009 (UW Report). Moreover, the Nuclear Magnetic Resonance ("NMR") analysis performed by the UW lab was not capable of establishing that the chemical purity of the UW solid was similar to that of the oil obtained by Larsson. "At best NMR done properly can get down to 1 percent impurity . . . . If not done exactly properly, it may – it may not show even that level of purity. So NMR, it's not a technique of characterization to assign purity." Trial Tr. (Atwood Direct) 921:6-24. In order to determine the chemical purity of the solid it obtained, the UW lab would have needed to perform achiral HPLC, which it did not do. *Id.*

337. Because nothing in the record establishes the chemical purity of the solid obtained by Dr. Elder, it is impossible to know whether the UW lab faithfully replicated Example 22 of Larsson even up to the workup stage of the Example. *See* Trial Tr. (Atwood Direct) 918:15-919:5.

338. In summary, because Dr. Elder did not replicate Example 22 with sufficient fidelity to obtain the oil Larsson describes and because the chemical purity of the solid that he did obtain is unknown, his experiment does not indicate that one skilled in the art could have converted that oil

into an amorphous solid. Instead, with the benefit of hindsight knowledge that a solid amorphous dexlansoprazole compound could be obtained, Dr. Elder – a person of extraordinary skill in the art with more than a decade of subsequent knowledge regarding asymmetric oxidation reactions – conducted an experiment different than that described in Larsson and different from how the ordinarily skilled person in 1998 would have approached the Larsson reference.

339. For all of the above reasons, one skilled in the art would not have been able to make solid amorphous dexlansoprazole based on the disclosures of Barberich without considerable and undue experimentation.

b. Handa and TWi's Contention that Larsson and Barberich II Anticipate a Salt of an Amorphous Compound of Dexlansoprazole

340. Handa and TWi also contend that Larsson and Barberich II anticipate a salt of an amorphous compound of dexlansoprazole. At trial, they did not present any testimony by their own experts in support of this assertion. Rather, they rely on the testimony of Dr. Kamiyama that as of June 1999 it was possible to make an amorphous salt of dexlansoprazole from an oil. Handa, Par and TWi's Post-Trial Brief at 42 (citing Trial Tr. (Kamiyama Cross) 131:12-18).

341. The disclosure of salts in Larsson and Barberich II cited by Handa and TWi is the same. In particular, Larsson refers to creation of salts using "conventional processes" and Barberich II incorporates Larsson's disclosure. *See* TX0070-0054 (Larsson I) ("and the obtained sulfoxide optionally is converted into a pharmaceutically acceptable salt by conventional processes"); TX0078-0003 (Barberich II) at [13] (incorporating disclosures of Larsson I as to "[s]yntheses of R(+) lansoprazole and S(-) lansoprazole by asymmetric oxidation and by bioreduction"); TX0301-0005 (Larsson II) at 7:59-61 ("The compounds defined by the above formulas . . . may be converted into pharmaceutically acceptable salts thereof by conventional methods"). Larsson and Barberich do not specifically address how these salts are made. Similarly, the '282 Patent does not describe how to make an amorphous salt. Trial Tr. (Kamiyama Direct) 130: 8-10. However, as noted above, Dr. Kamiyama testified that a person of skill in the art in 1999 would have known how to obtain a salt of dexlansoprazole starting with an oil.

342. Nonetheless, Dr. Kamiyama's testimony does not establish that a person of ordinary skill

in the art in 1999 would have known how to obtain a solid amorphous dexlansoprazole salt based on Larsson or Barberich II, as claimed in the '282 Patent. Testimony at trial established that a salt obtained from an oil of dexlansoprazole may or may not be solid. *See* Trial Tr. (Rogers Cross) 678:12-18 (testifying that he has obtained salts as oils); TX 0700-0007 (U.S. Patent No. 7,271,182) at col.3, ll.31-33 (another patent listing Dr. Kamiyama as an inventor which specifically states that the form of the dexlansoprazole salt of his invention was "not particularly limited and may be an oil, a non-crystal, or a crystal"). Consequently, the disclosure of salts of dexlansoprazole in Larsson and Barberich does not constitute clear and convincing evidence that it was possible in June 1999 to make an amorphous solid salt of dexlansoprazole.

343. Further, Dr. Kamiyama's testimony that in June 1999 it would be have been possible to make an amorphous salt of dexlansoprazole from an oil of dexlansoprazole, *see* Trial Tr. (Kamiyama Cross) 131:2-4, is consistent with this conclusion because he did not testify that the resulting salt would necessarily have been a solid. Indeed, the evidence at trial established that a salt obtained from an oil might itself be an oil, as discussed above. Dr. Kamiyama's testimony was also consistent with the evidence presented at the summary judgment stage, demonstrating that an amorphous salt in oil form might be obtained from a starting material that is an oil.

344. For all of these reasons, Defendants have failed to establish by clear and convincing evidence that Larsson and Barberich II anticipate a salt of an amorphous compound of dexlansoprazole.

2. Obviousness

a. The Level of Ordinary Skill in the Art of the '282 Patent

345. The '282 Patent is directed to the art of solid-state pharmaceutics, and in particular the fields of chemistry, chemical engineering, or related disciplines. The Court finds that the level of skill in the art of the invention of the '282 Patent is a bachelor's degree in chemistry, chemical engineering, or related disciplines, with a minimum of three years of experience in the pharmaceutical industry related to organic synthesis, API (active pharmaceutical ingredient) manufacturing, crystallization or detection and/or evaluation of solid-state forms, or an advanced degree in chemistry, chemical engineering, or related disciplines, with less or no industry

experience. *See* Trial Tr. (Atwood Direct) 902:3-7.

b. Handa and TWi's Contention that Claims 1 and 2 of the '282 Patent are Obvious over the Larsson, Von Unge, and Barberich II References in View of the Knowledge of One of Ordinary Skill in the Art

346. Handa and TWi contend that it would have been obvious for one ordinarily skilled in the art in 1999 to evaporate the oil described in Larsson and Von Unge (and incorporated by reference in Barberich) using known techniques to obtain an amorphous solid.

347. For the same reasons discussed above in connection with the Crystal-Form Patents, however, the person of ordinary skill in the art in 1999 would not have had a reasonable expectation that the oily form of dexlansoprazole described by the Larsson and Von Unge references could be evaporated to obtain an amorphous solid. To the contrary, the Larsson and Von Unge references demonstrate the difficulty of obtaining any solid forms of dexlansoprazole.

348. As demonstrated by other experiments set forth in the Larsson and Von Unge references, the Larsson inventors possessed greater than ordinary skill in the art. *See* Trial Tr. (Atwood Direct) 945:6-946:14. One skilled in the art reasonably would infer from the fact that the Larsson inventors' stated goal was to synthesize large quantities of compounds for pharmaceutical compounds, and the fact that they successfully synthesized other compounds as crystals, that Larsson and Von Unge sought to produce a crystal form of dexlansoprazole but failed. In addition, the Larsson inventors were able to obtain enantiomeric crystals of omeprazole and compounds (Ib), (Ic), and (Ie), as well as solids of compounds (Ib), (Ic), and (Ih). Nevertheless, the Larsson inventors failed to obtain dexlansoprazole or (S-)-lansoprazole in a solid form.

349. Moreover, the oil of dexlansoprazole obtained by Larsson before the acetonitrile purification steps had a high chemical purity (99.9% achiral analysis). *See* TX 0301-0010 (Larsson II) at col.18, ll.26-35. One of skill in the art would have understood that acetonitrile is toxic and must be removed before it can be used in a pharmaceutical composition. *Id.* (Rogers Cross) 670:11-22. Moreover, acetonitrile is a highly volatile solvent, which evaporates in a short time if merely left sitting in an open container. *Id.* (Rogers cross) 669:24-670:10; *id.* (Atwood direct)

924:9-11 ("Acetonitrile is so volatile if we just took a small cap of acetonitrile and put it on the bench top, within about ten minutes it's all gone. It evaporates."). As evidenced by the UW test, the person of ordinary skill would have taken well-known steps to evaporate it, typically using a rotary evaporator under a vacuum to remove the acetonitrile following the purification steps. Trial Tr. (Rogers Cross) 669:1-670:10 (admitting that evaporating a solvent was a predictable process at the time of the Larsson reference, that acetonitrile is highly volatile and would evaporate at room temperature, and that the use of a rotary evaporator would have been known at the time of the Barberich reference); *id.* (Atwood Direct) 923:9-924:25 ("[I]t's not possible in this evaporation process to have acetonitrile trapped in the center of the oil in some fashion, because the oil is in constant motion as a fluid . . . ."). Accordingly, the person of ordinary skill reviewing the Larsson reference in 1999 would have concluded that the oil left after the acetonitrile steps did not contain any significant amount of acetonitrile and also had a high chemical purity.

350. For all of these reasons, the fact that Larsson had "a very pure sample" that nevertheless persisted as an oil would have discouraged the person of ordinary skill from attempting to dry the oil obtained by Larsson. *See id.* (Atwood Direct) 925:25-926:2.

351. In light of the purity reported for the dexlansoprazole obtained in Example 22, the person of ordinary skill also would not have understood that the oil of dexlansoprazole obtained by Larsson could be obtained using trituration, the process of "removing [an] impurity from a sample by treating it with a solvent." Trial Tr. (Atwood Direct) 925:1-12; *see id.* Trial Tr. (Rogers Cross) 670:23-672:1 ("I think from reading Example 22, if you were to obtain this exact oil, you wouldn't necessarily know how to remove all the remaining solvent.").

352. Further, the prior art references relied upon by Dr. Rogers for his opinion that trituration could be used to convert Larsson's oily dexlansoprazole to an amorphous solid of dexlansoprazole do not provide clear and convincing evidence that such a procedure would work. *See* TX 0146x15 (Zubrick); TX 0146x21 (Gadekar); TX 0146x20 (Castellano). Defendants offered no experimental evidence in which they actually attempted to triturate dexlansoprazole in oily form to obtain a solid. Moreover, the only reason for oiling out given in the Zubrick reference is that "the boiling point of the recrystallization solvent is higher than the melting point of the compound," TX

0146x15-0003 (Zubrick), which Dr. Rogers has admitted does not apply to any lingering acetonitrile solvent in dexlansoprazole because "the boiling point of the acetonitrile is pretty low," Trial Tr. (Rogers Cross) 672:17-673:2. Indeed, the Zubrick reference itself acknowledges that, "[s]ometimes, once a solid oils out, it doesn't want to solidify at all . . . ." TX 146x15-0004 (Zubrick). In addition, the method that Zubrick describes for obtaining a solid requires first obtaining crystals and then using those crystals as seeds to "[p]ossibly" solidify the remainder of the oil; however, Dr. Rogers admitted at trial that dexlansoprazole will not form crystals using this method. *Id.* (Rogers Cross) 675:13-676:9.

353. The Gadekar reference, TX 0146x21-0006 (Example 1), does not assist because it describes trituration of a completely different compound – 5-methyl-1-phenyl-2-(1H)-pyridone – using petroleum ether, a solvent that is not included in any of Defendants' references as having ever been used with dexlansoprazole. *See* Trial Tr. (Rogers Cross) 676:23-677:11. The Castellano reference, TX 0146x20-0001, describes the trituration of an oily solid with methanol; however, Dr. Kamiyama tried unsuccessfully to crystallize dexlansoprazole from methanol, *see* Trial Tr. (Kamiyama Direct) 110:22-111:3, indicating that methanol likely would not have worked as a trituration solvent for the dexlansoprazole oil obtained by Larsson.

354. Most fundamentally, trituration is a technique designed to remove an impurity. Trituration does not work where, as in Larsson, the sample is very pure. *Id.* (Atwood Direct) 926:3-12.

355. Thus, one of ordinary skill in the art at the time of the '282 Patent would have concluded from the fact that Example 22 discloses the synthesis and production of an oil rather than a solid of dexlansoprazole "either the dexlansoprazole is, in fact, a liquid at room temperature, or that it's going to be very, very difficult to convert it to a solid form." Trial Tr. (Atwood Direct) 926:13-22; *cf. id.* (Rogers Cross) 678:9-679:2 ("I understand that some compounds in all chemistry can exist at room temperature as a liqu*id.* If the viscosity is high enough, somebody could call it an oil.").

356. Further, the inventors of the '282 Patent "added hexane quickly" to prevent the decomposition of the dexlansoprazole in concentrated fractions recovered from the chiral column used for the separation of lansoprazole into its enantiomers in Reference Example 1. *See* Trial Tr. (Atwood Direct) 961:1-18. That hexane could stabilize dexlansoprazole to prevent decomposition

was "completely unpredictable" at the time the '282 Patent was filed in June 1999. *Id.* (Atwood Direct) 961:1-18. Similarly, in Reference Example 2, triethylamine was used to prevent composition of the concentrated dexlansoprazole solution. Cf. *id.* (Kamiyama Direct) 106:18-108:4; *see* also TX 0722-0002 (SSCI document entitled "Standard Polymorph Screen") ("TAK-390 [dexlansoprazole] degraded in solution over time but was stabilized by addition of triethylamine.").

357. For these reasons, the person of ordinary skill in the art would not have had a reasonable expectation that the oily form of dexlansoprazole disclosed by Larsson and Von Unge could be completely evaporated to an amorphous solid.

c. Handa and TWi's Contention that Claim 1 of the '282 Patent is Obvious in View of Larsson, Von Unge, or Barberich II in Combination with Takechi, Brittain, and/or Bohlin

358. Handa and TWi further contend that asserted claim 1 of the '282 Patent is obvious in view of Larsson, Von Unge, or Barberich II in combination with Takechi, Brittain, and/or Bohlin.[6] The Larsson, Von Unge, Barberich, and Bohlin references are discussed above in connection with Defendants' validity challenges to the Crystal-Form Patents.

359. "Takechi," TX 0388, refers to U.S. Patent No. 5,536,735.

360. "Brittain," TX 0387, refers to J. Keith Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids," in *Polymorphism in Pharmaceutical Solids* (Harry G. Brittain, ed., 1999).

i. The Disclosure of Takechi

361. The Takechi reference discloses pharmaceutical compositions comprised of a benzimidazole compound, such as racemic lansoprazole, and a stabilizing excipient such as nicotinamide or benzamide. *See* TX 0388-0002 (Takechi) at col.1, ll.50-67. The pharmaceutical compositions disclosed in Takechi may be solid or liqu*id. See id.* at TX 0388-0008, claim 8

[6] Dr. Rogers further testified that Borner, TX 0075-0001, demonstrates that the compound dexlansoprazole was known at the priority date of the '282 Patent and could be separated using chromatography. See Trial Tr. (Rogers Direct) 581:9-582:1. However, nothing in Borner (or any other prior art reference) discloses dexlansoprazole as a solid. See TX 0075; Trial Tr. (Atwood Direct) at 1057:16-1058:10.

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(lyophilizate) and claim 9 (aqueous solution). Takechi discloses that "[t]he solid composition may, for example, be a solid preparation obtainable by freeze-drying or spray-drying the above aqueous solution . . . . The preferred solid preparation is a lyophilizate." TX 0388-0005 (Takechi) at col.7, l.56 to col.8, l.3. A lyophilizate is the product of freeze-drying, a dehydration process used to preserve a chemically unstable material. *See* Trial Tr. (Atwood Direct) 929:1-15. Lyophilization typically is used to remove solvents by vaporization. *See id.* (Rogers cross) 683:19-22; TX 0387-0005 to -0007 (Brittain).

362. Examples 4, 5, and 6 of Takechi specifically disclose lyophilized preparations of racemic lansoprazole with nicotinamide and with various other excipients such as sodium hydroxide (Examples 4, 5, and 6), Pluronic F68 (Examples 4 and 6), and citric acid, disodium hydrogenphosphate, sodium hydrogen carbonate, and mannitol (all included in Example 6). *See* TX 0388-0007 (Takechi) at col.12. For instance, in Example 4, lansoprazole, nicotinamide, and Pluronic F68 (a polymer) "were blended in powdery form and, then, dissolved in" sodium hydroxide. This solution was then filtered and distributed in small portions into vials, where it was then lyophilized (freeze-dried).

363. The racemic lansoprazole used by Takechi as starting material is in solid form. *See* Trial Tr. (Atwood Direct) 929:23-930:3; *see* also TX 0388-0007 (Takechi) at col.12 (stating in each of Examples 3, 4, 5, and 6 that the starting material included three kilograms of lansoprazole). However, Takechi does not disclose whether the lyophilized preparations of racemic lansoprazole that he obtains are amorphous or crystalline. Trial Tr. (Atwood Direct) 929:16-22; *id.* (Rogers Cross) 686:1-4. Further, Takechi does not teach any method of freeze-drying without first combining the racemic lansoprazole with nicotinamide or other excipients, suggesting that such preparations were either not attempted or were not stable. *See id.* (Rogers Cross) 684:25-686:5.

364. One would not obtain the same form of lyophilizate if the starting material was an oil rather than a solid. Trial Tr. (Atwood Direct) 930:4-14 ("[I]f we're starting with instead of solid dexlansoprazole, an oil of lansoprazole, then we're going to have an oil left at the end of the process."). The person of ordinary skill also would have understood that lyophilization is designed to remove solvent, and that it would not work to form an amorphous solid where the starting

material is a very pure oil, as was the case with the oil of dexlansoprazole described in Example 22 of Larsson.

365. The person of ordinary skill in 1999 thus would not have known from Takechi how to lyophilize the oily form of dexlansoprazole disclosed in Larsson and Von Unge to obtain an amorphous solid.

ii. The Disclosure of Brittain

366. The Brittain publication describes general methods for synthesizing amorphous solids. Trial Tr. (Atwood Direct) 928:11-19. Brittain does not describe any methods for obtaining an amorphous solid from an oil. *Id.* (Atwood Direct) 927:16-22 ("There is no teaching in Brittain that one starts with a liquid, an oil, and renders that amorphous."). Rather, Brittain discloses methods that "avoid the thermodynamically preferred crystallization process" or that "disrupt[] an existing crystal structure" – the implication being that these are methods that a person of ordinary skill would turn to when the crystalline form is known to be available and an amorphous solid is desired. *See* TX 0387-0004 (Brittain).

367. Thus, for example, Brittain discloses techniques that are commonly used to obtain an amorphous solid after the compound of interest has already been crystallized, including: (1) Solidification of the melt, in which an amorphous solid is "created by rapidly *cooling a liquid* so that crystallization nuclei can neither be created nor grow sufficiently" (TX 0387-0004 (Brittain). at TX 0387-0004) (emphasis added); (2) Spray-drying, in which the compound of interest is added to a *solvent or slurry [i.e., a watery mixture of insoluble solid material],* which is then atomized (reduced to minute particles or a fine spray), and then "dried in the airstream in seconds owing to the high surface area in contact with the drying gas" (*id.* at TX 0387-0005) (emphasis added); (3) Lyophilization, "a particularly useful technique in the case of compounds that are susceptible to decomposition in the presence of moisture but that are more stable as dry solids. . . . [L]yophilization also can be employed to *convert crystalline materials into their amorphous counterparts*. . . . [R]apid freezing is employed so as to avoid the crystallization process." (*id.* at TX 0387-0005-7) (emphasis added); (4) Removal of solvent from a *crystalline* solvate or hydrate (*id.* at TX 0387-0007) (emphasis added); and (5) *Precipitation* from solution, in which "the level

of supersaturation is carefully controlled . . . to avoid crystallization . . . ." (*id.* at TX 0387-0009) (emphasis added). The last of these methods, precipitation, was used by Larsson and Von Unge, but resulted in an oil and not a solid. Other techniques disclosed in Brittain require solid starting material. The first method, solidification of the melt, consists of heating a solid material above its melting point, then rapidly cooling the resulting liquid so that it forms an amorphous compound before crystallization can occur. However, no evidence was presented at trial of this method ever being attempted to obtain an amorphous solid of dexlansoprazole, or even any related compound. Spray-drying and lyophilization (freeze-drying) work by removing solvent from the compound of interest in order to render it an amorphous solid. *See* Trial Tr. (Rogers Cross) 680:22-25 (spray-drying); *id.* 683:19-22 (lyophilization). Thus, they are simply alternatives to evaporation, the technique attempted unsuccessfully by Larsson to obtain a solid. As discussed above, acetonitrile is a highly volatile solvent that evaporates at room temperature that would already have been removed from the dexlansoprazole Larsson synthesized in Example 22 through normal evaporation methods. Accordingly, as Dr. Atwood testified, using Larsson's oil for spray-drying would result in "an oily mess rather than a dry material at the end of the process." Trial Tr. (Atwood Direct) 927:23-928:10. Consequently, one skilled in the art would not have expected spray-drying or lyophilization to change the oil of Larsson into an amorphous solid. Accordingly, the person of ordinary skill would not have concluded that the techniques disclosed by Brittain could be used to convert the oil of dexlansoprazole disclosed in Larsson and Von Unge to an amorphous solid. Nor, as mentioned above, have Defendants performed any experiments or pointed to any publications to indicate that these methods could be used successfully to make amorphous dexlansoprazole.

iii. The Disclosure of Bohlin

368. As discussed above in connection with the Crystal-Form Patents, Bohlin discloses, among other things, the synthesis of esomeprazole as an amorphous solid. *See* TX 0076-0011 to -0012 (Bohlin) at Example 1. Bohlin acknowledges that the prior art already disclosed synthesis of esomeprazole (the neutral, non-salt form) only as "a syrup or oil." *See id.* at TX 0076-0003 to -0004.

369. The synthesis of esomeprazole described in Example 1 of Bohlin is a complicated process. He starts with a sodium salt of esomeprazole. This esomeprazole salt was dissolved in water and then methylene chloride was added. Dr. Atwood explained that methylene chloride is "more dense than water and doesn't mix with water. So one then has on the bottom a methylene chloride layer, an organic phase, and on top the aqueous, the water phase, with the sodium salt of esomeprazole." Acetic acid was then added, which converted the esomeprazole from a salt into a neutral molecule. The neutral molecule was no longer soluble in water, and so it was extracted into the organic phase. The organic phase was then separated and the methylene chloride evaporated under vacuum to obtain a concentrated solution of esomeprazole in methylene chloride. Next, iso-octane was added and the solvent was evaporated again until an almost dry, amorphous solid substance was formed. This procedure was essentially repeated to obtain solid amorphous neutral esomeprazole. *See* TX 0076-0011 to -0012 (Bohlin) at Example 1; Trial Tr. (Rogers Cross) 687:24-689:18; *id.* (Atwood Direct) 931:1-932:22.

370. One of skill in the art at the time of the '282 Patent would not have reasonably expected that the Bohlin method could be used successfully to make amorphous dexlansoprazole as there was no evidence that methylene chloride, the solvent used in Bohlin, could be used as an effective solvent for dexlansoprazole. Nor was there any evidence presented at trial that Bohlin's complicated process for making amorphous esomeprazole could be used to make amorphous dexlansoprazole. *Id.* (Rogers Cross) 689:19-22; *id.* (Atwood Direct) 933:7-10.

371. Accordingly, the Court finds that one skilled in the art would not have had a reasonable expectation, in June 1999, that an amorphous compound of dexlansoprazole could be obtained in view of Larsson, Von Unge, or Barberich II in combination with Takechi, Brittain, and/or Bohlin.

d. Handa's and TWi's Contention that Claim 2 of the '282 Patent is Obvious over the Larsson and Von Unge References in Combination with Barberich II, the PDR Entry for Prevacid, and/or Katsuki

372. Handa and TWi further contend that asserted claim 2 of the '282 Patent is obvious in view of Larsson or Von Unge in combination with Barberich, the Physicians' Desk Reference ("PDR") entry for Prevacid from 1997, and/or Katsuki.

373. Trial Exhibit 120x08 is the PDR entry for Prevacid from 1997 (specifically, PDR 2746-48

(51st ed. 1997)). This PDR entry describes the use of racemic lansoprazole to treat patients. Handa and TWi do not contend that this reference teaches any relevant methods for isolating dexlansoprazole as an amorphous solid, but only that the R- and S-enantiomers of lansoprazole "can be made into a composition that's a medicine." Trial Tr. (Rogers Cross) 690:1-13.

374. Katsuki compares the "pharmacokinetics of the [R(+) and S(-) enantiomers of lansoprazole] in humans." TX 0513-0001. Dr. Rogers testified that Katsuki discloses "superior pharmacokinetics for [] dexlansoprazole, the R-isomer as opposed to the S-isomer," Trial Tr. (Rogers Direct) 597:3-8. In particular, Table 2 in Katsuki shows that "the level of dexlansoprazole in the blood is higher for the R-isomer than the S-isomer." *Id.* (Rogers Direct) 597: 14-17. Dr. Rogers conceded, however, that he did not know whether the drug that is bound to plasma proteins and thus measured in blood concentrations (as shown in Table III of Katsuki at TX 0513-0004) is available to exert therapeutic effect by binding to proton pumps in the parietal cells. *Id.* (Rogers Cross) 691:5-693:6. In fact, Katsuki states that this greater protein-binding affinity may *inhibit* the ability of the R-enantiomer to bind to the compartment of interest, namely, the parietal cells of the stomach. *See* TX 0513-0004 ("The binding to human serum proteins was significantly greater for R(+)-enantiomer than for S(-)enantiomer . . . . Distribution of a drug to compartments other than serum is limited by the drug binding to plasma proteins such as albumin and α1 acid glycoprotein. . . . Consequently, the R(+)-enantiomer which is extensively bound to albumin may be poorly distributed and slowly eliminated, resulting in the higher serum concentrations than those of the S(-)enantiomer."). When Dr. Rogers was asked to reconcile these statements in Katsuki with his opinion that a person of skill in the art would read Katsuki as showing that the R-isomer has superior pharmacokinetics over the S-isomer of lansoprazole, Dr. Rogers testified that he was unable to do so because he is not an expert in pharmacokinetics. Trial Tr. (Rogers Cross) 691:5-693: 6. Therefore, the Court finds Dr. Roger's characterization of Katsuki as demonstrating the pharmacokinetic advantages of dexlansoprazole over the S-isomer to be unpersuasive.

e. Motivation to Obtain Dexlansoprazole as an Amorphous Solid

375. As discussed above, Barberich II disclosed the advantages of dexlansoprazole over the

racemic lansoprazole for treating GERD and therefore provided a person of skill in the art a motivation to make a pharmaceutical composition of dexlansoprazole and a "pharmaceutically acceptable excipient, carrier or diluent."

376. Similarly, Larsson would have provided a motivation to create a pharmaceutical composition of dexlansoprazole to the extent that it teaches that "[t]he single enantiomers of pharmacologically active compounds have met an increased interest in the last years because of improved pharmacokinetic and biological properties." TX-0301-0002, col. 1, ll. 48-51.

377. At the time of the invention, it was known that crystalline compounds are generally preferable to amorphous compounds for use in pharmaceuticals. *See* Trial Tr. (Genck Direct) 771:7-10 ("[I]t is known that crystalline compounds are more stable and, thus, preferred for pharmaceutical formulations."); *id.* (Atwood Direct) 896:16-897:12 (testifying that "[t]he crystalline state is the preferred solid-state" for pharmaceutical compositions, and that all of the brand-name proton pump inhibitors on the market use crystalline API); *id.* (Rogers Cross) 700:9-13 (admitting same).

378. Nonetheless, there are at least two reasons why researchers seeking to develop dexlansoprazole as a pharmaceutical would have been motivated to obtain dexlansoprazole as an amorphous compound. First, as Takeda concedes, obtaining solid amorphous dexlansoprazole was "a necessary first step in obtaining a crystal form of the compound." *See* Takeda's Post-Trial Findings of Fact and Conclusions of Law, No. 48 (citing TX 1055 ('282 Patent) at col. 7 l. 51 - col. 8, l. 7 Reference Example 1); *id.*, col. 8, ll. 9-29 (Reference Example 2)). Thus, development of a technique for obtaining the amorphous form would also be valuable in developing pharmaceuticals using the crystal form of dexlansoprazole. Second, although it was understood that in general the amorphous form of a compound was less desirable than a crystal form for use in pharmaceuticals, the prior art taught that the amorphous form would have advantages over the oil or liquid form and might even have certain advantages over the crystal form. *See* TX0076 (Bohlin) at 2:1-4, 8, 14- 16 (teaching that a syrup or oil is "unsuitable for pharmaceutical use because of the difficulty of handling an oil and incorporating it into solid pharmaceutical compositions, especially in a reproducible manner"); TX0387-0003 (Brittain) (teaching that

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amorphous solids are sometimes preferred over crystalline form for pharmaceuticals because they undergo dissolution at a faster rate).

379. Accordingly, one of ordinary skill in the art in 1999 would have been motivated to obtain an amorphous solid of dexlansoprazole, as well as a pharmaceutical composition using such a solid.

3. Handa's and TWi's Contention that the Claims of the '282 Patent are Invalid for Failure to Satisfy the Written Description Requirement

380. As noted above, Handa and TWi contend that the asserted claims of the '282 Patent are invalid for failure to satisfy the written description requirement because the specification of the '282 Patent contains no written description of 1) an amorphous (as opposed to crystalline) compound of dexlansoprazole; and 2) a salt of amorphous dexlansoprazole.

381. As to the first argument, the Court finds that a person of ordinary skill reviewing the '282 Patent specification would understand that the inventors were in possession of an amorphous solid of dexlansoprazole based on Reference Examples 1 and 2, which describe the isolation of amorphous solids of dexlansoprazole.

382. The Court expressly rejected the second argument at summary judgment, holding that the disclosure of the '282 Patent "shows that the inventors were in possession of the claimed salt of dexlansoprazole." TWi Summary Judgment Order [D.N. 235] at 45. The Court declines to revisit that ruling.

III. CONCLUSIONS OF LAW

A. Constitutional Standing of the Takeda U.S. Entities

383. Under Article III, § 2 of the U.S. Constitution, the jurisdiction of federal courts is limited to "Cases" or "Controversies." To establish constitutional standing under this provision, a party "must 'show that the conduct of which [it] complains has caused [it] to suffer an "injury in fact" that a favorable judgment will redress.'" *WiAV Solutions LLC v. Motorola, Inc.*, 631 F.3d 1257, 1264 (Fed. Cir. 2010) (quoting *Elk Grove Unified Sch. Dist. v. Newdow*, 542 U.S. 1, 11 (2004)). In a patent case, injury in fact may be established by demonstrating that a party has been deprived of exclusionary rights created under the Patent Act. *Id.* at 1264-1265. Thus, "a party holding one or

more of those exclusionary rights – such as an exclusive licensee – suffers a legally cognizable injury when an unauthorized party encroaches upon those rights and therefore has standing to sue." *Id.* at 1265-1266 (citing *Morrow v. Microsoft Corp.*, 499 F.3d 1332, 1340 (Fed. Cir.2007); *Intellectual Property Development, Inc. v. TCI Cablevision of California, Inc.*, 248 F.3d 1333, 1346 (Fed. Cir. 2001)); *Ortho Pharma. Corp. v. Genetics Inst., Inc.*, 52 F.3d 1026, 1031 (Fed. Cir.1995)).

384. While a transfer of title in the patent confers constitutional standing on the assignee to sue another for patent infringement in its own name, a nonexclusive license does not confer standing on the licensee because it is merely a "bare" license – that is, a promise by the patent owner not to sue the licensee for making, using or selling the patented device where the patent owner reserves the right to grant similar licenses to other entities. *Intellectual Property Development, Inc. v. TCI Cablevision of California, Inc.*, 248 F.3d at 1345. In other words, a nonexclusive license does not convey to the licensee any of the exclusionary rights afforded patent owners under the Patent Act. Somewhere between these two extremes is an exclusive license. "An exclusive licensee receives more substantial rights in a patent than a nonexclusive licensee, but receives fewer rights than an assignee of all substantial patent rights." *Id.* For example, a licensee may be granted exclusive rights in a particular field of use. A licensee holding exclusive rights only in a particular field of use under the patent has standing to sue so long as the patent owner is also joined in the action as a co-plaintiff. *See Int'l Gamco, Inc. v. Multimedia Games, Inc.*, 504 F.3d 1273, 1278-1279 (Fed. Cir. 2007). This requirement arises from the doctrine of "prudential standing" rather than constitutional standing and is intended to address the potential "risk of multiple suits and multiple liabilities against an alleged infringer" where both an exclusive licensee and a patent owner may assert infringement claims for a single act of infringement. *Id.*

385. A license is "exclusive" if the licensee is "a beneficial owner of some identifiable part of the patentee's bundle of rights to exclude others." *Ortho Pharm. Corp. v. Genetics Inst., Inc.*, 52 F.3d 1026, 1032 (Fed. Cir.1995). "To be an exclusive licensee for standing purposes, a party must have received, not only the right to practice the invention within a given territory, but also the patentee's express or implied promise that others shall be excluded from practicing the invention

within that territory as well." *Rite-Hite Corp. v. Kelley Co., Inc.*, 56 F.3d 1538 (Fed. Cir. 1995) (citations omitted). The licensee need "only be able to exclude 'others,' not all others." *Abbott Laboratories v. Sandoz, Inc.*, 2010 WL 1948185, *3 (N.D.Ill., May 12, 2010) (quoting *Ropak Corp. v. Plastican, Inc.*, No. 04–C5422, 2005 WL 2420384, at *2–3 (N.D.Ill. Sept.30, 2005) (citing *Ortho Pharm.*, 52 F.2d at 1032); citing *Hill Phoenix Inc. v. Systematic Refrigeration, Inc.*, 117 F.Supp.2d 508, 512 (E.D.Va. 2000)). To determine whether a license is exclusive, the court must look beyond labels and examine the terms of the parties' agreement to determine whether they intended to create an exclusive license. *Textile Productions, Inc. v. Mead Corp.*, 134 F.3d 1481, 1484 (Fed. Cir. 1998).

386. The Court has examined the terms of the License Agreement. As stated in its Findings of Fact, the Court finds that the License Agreement grants TPNA exclusive rights to the patents covering dexlansoprazole, including the '282 Patent, so that TPNA may sell TPC's drug products in the United States *and* exclude others from selling generic dexlansoprazole products, including those that contain amorphous dexlansoprazole. Because the rights of the other Takeda U.S. entities, TPA and Takeda LLC, are derivative of TPNA's rights, those entities have the same rights. As a result, the Takeda U.S. entities can block TWi from obtaining a license from TPC to practice the '282 Patent in connection with the ANDA products. In other words, the Takeda U.S. entities hold at least *some* of the rights in the patent owner's bundle of exclusionary rights under the Patent Act. Further, to the extent the License Agreement is a "field of use" agreement, the Takeda U.S. entities have prudential standing because TPC is joined in the action, thus meeting the standing requirements of *Int'l Gamco*. Accordingly, the Court concludes the Takeda U.S. entities have standing to assert infringement under the '282 Patent.

B. Declaratory Judgment Jurisdiction

387. Declaratory judgment jurisdiction exists in a patent case if there is an actual controversy, that is, the "facts alleged, under all the circumstances, show that there is a substantial controversy, between parties having adverse legal interests, of sufficient immediacy and reality to warrant the issuance of a declaratory judgment." *MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. 118, 127 (2007) (internal quotation marks omitted). The question of whether there is an actual controversy

is evaluated "in the context of the facts as they existed when the complaint was filed." *Telectronics Pacing Systems, Inc. v. Ventritex, Inc.,* 982 F.2d 1520, 1527 (Fed. Cir. 1992).

388. Even where there is an actual controversy, the exercise of a court's jurisdiction over a declaratory judgment action is discretionary. *Minnesota Mining and Mfg. Co. v. Norton Co*., 929 F.2d 670, 672 (Fed. Cir. 1991). In *Minnesota Mining*, the Federal Circuit offered the following guidance as to when the exercise of discretion is appropriate:

> The reason for giving this discretion to the district court is to enable the court to make a reasoned judgment whether the investment of judicial time and resources in a declaratory action will prove worthwhile in resolving a justiciable dispute. Situations justifying exercise of the court's discretion to issue a declaratory judgment include "(1) when the judgment will serve a useful purpose in clarifying and settling the legal relations in issue, and (2) when it will terminate and afford relief from the uncertainty, insecurity, and controversy giving rise to the proceeding." E. Borchard, Declaratory Judgments, 299 (2d ed. 1941).

Id. at 672-673. Some courts have declined to exercise jurisdiction under the Declaratory Judgment Act over claims asserting future infringement under § 271(a) based on the filing of an ANDA by a generic manufacturer, reasoning that permitting such an action would undermine Congress's intent in creating a safe haven under § 271(e)(1). *See Intermedics, Inc. v. Ventritex, Inc.*, 775 F.Supp. 1269, 1290 (N.D.Cal.1991), *aff'd,* 991 F.2d 808 (Fed.Cir.1993) (unpublished disposition); *Abbott Laboratories v. Zenith Labs., Inc.*, 934 F.Supp. 925, 938 (N.D. Ill., 1995).

389. The question of whether a declaratory judgment claim under § 271(a) based on the filing of an ANDA is consistent with the statutory scheme established under the Hatch-Waxman Act is the subject of considerable disagreement among the lower courts and has not been addressed in any precedential opinion by the Federal Circuit. In *Cephalon, Inc. v. Sandoz, Inc.,* for example, Judge Robinson opined, "I do not understand the administrative paradigm of the Hatch-Waxman Act to preclude a patent holder from establishing jurisdiction under 28 U.S.C. § 2201(a)." 2012 WL 682045, at *5 (D.Del., Mar. 1, 2012); *see also In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation,* 693 F. Supp. 2d 409, 418-419 (D.Del., 2010) ("A claim for declaratory judgment under 35 U.S.C. § 271 "is proper so long as plaintiffs can show the existence of real and immediate controversy. . . . Moreover, "[i]n the context of a § 271(e)(2) infringement action, where the court is engaged in a forward-looking analysis of what defendants will do upon

ANDA approval, defendants' declared intent is sufficient to make the controversy real and immediate.") (citation omitted). In contrast, in *In re Rosuvastatin Calcium Patent Litig.*, Judge Stark stated, "to permit the § 271(a) action to proceed seems to me to be inconsistent with Congressional intent." 2008 WL 5046424, at *13 (D.Del. Nov. 24, 2008). He reasoned:

> Congress evidently believed that a patentee in AstraZeneca's position did not have a cause of action under § 271(a) – indeed, the lack of such an action was a motivating factor in creating the § 271(e)(2) action. Second, the § 271(e)(1) "safe harbor" would be threatened if a patentee could sue ANDA filers under § 271(a) for conduct (such as preparing an ANDA) that is expressly identified in the Act as "not ... an act of infringement."

Id.; *see also Eisai Co., Ltd. v. Mutual Pharmaceutical Co., Inc.*, 2007 WL 4556958, at *17 (D.N.J., Dec. 20, 2007) ("[A]ctivities protected by the safe harbor provision [of § 271(e)] cannot serve as the basis for a declaratory judgment of actual future infringement").

390. Courts that have addressed whether a § 271(a) claim based on the filing of an ANDA raises a sufficiently immediate controversy to give rise to jurisdiction under the Declaratory Judgment Act have considered a variety of factors, including whether the generic manufacturer intends to market the drug, the likelihood or imminence of FDA approval and whether there is an automatic stay in place under the Hatch-Waxman Act. *See, e.g., Cephalon, Inc. v. Sandoz, Inc.*, 2012 WL 682045, at *5 (D.Del., Mar. 1, 2012)(finding declaratory judgment jurisdiction on the basis that there could be "no dispute" that the defendant was "systematically attempting to meet the applicable regulatory requirements while preparing to manufacture its product"); *Abbott Laboratories*, 934 F. Supp. at 938 (finding that controversy was not sufficiently immediate because even though FDA approval might be granted within three months of date complaint was filed, there was "no guarantee that the FDA approval will be forthcoming on any particular date in the future" and because the defendant might "change its course of actions and decide not to market the drug"); *In re Rosuvastatin Calcium Patent Litig.* 2008 WL 5046424, at *12 (D.Del. Nov. 24, 2008) (holding that controversy was not sufficiently immediate because 30 month stay of FDA approval was in place under Hatch-Waxman Act and was not set to expire until several months after the date scheduled for trial in that case).

391. In this case, Takeda has made no showing as to TWi's intent to bring its generic drug to

market or the likelihood of FDA approval. Rather, to establish declaratory judgment jurisdiction it relies entirely on the fact that TWi filed an ANDA. Further, the parties appear to disagree as to the likely timing of the FDA's approval in this case. Takeda suggests FDA approval could occur at any time because "no 30-month stay of approval of TWi's ANDA results from Takeda's assertion of the '282 Patent against TWi, in light of the fact that the '282 Patent is not listed in the Orange Book." *See* Takeda's Post-Trial Proposed Findings of Fact and Conclusions of Law, No. 434. In contrast, TWi states that "because TWi was not the first filer for either dosage strength of the ANDA product, FDA is prohibited from finally approving TWi's ANDA until six months after the first filer launches its ANDA product or otherwise loses its statutory exclusivity." Handa, Par, and TWi's Joint Post-Trial Brief Concerning Invalidity at 61. The immediacy of the controversy was not addressed at trial, and though the parties addressed the issue in their pre- and post-trial briefs the parties did not request argument on the question and the Court heard none.

392. In light of the scant record in this case as to the immediacy of the controversy and the minimal briefing provided by the parties on this issue, the Court is reluctant to exercise Declaratory Judgment jurisdiction over Takeda's § 271(a) claim even assuming that there may be an actual controversy. The Court is particularly concerned about deciding this question on a limited record because Takeda's § 271(a) claim asserted under the Declaratory Judgment Act implicates important and unresolved questions as to the interaction between the Declaratory Judgment Act and the Hatch-Waxman Act. The Court further finds that resolution of Takeda's infringement claim under § 271(a) and the Declaratory Judgment Act will not "serve a useful purpose in clarifying and settling the legal relations in issue" because the Court has already found that it has jurisdiction over Takeda's infringement claims under the Hatch-Waxman Act. Therefore, "the investment of judicial time and resources" required to decide whether the Court may decide Takeda's § 271(a) claim under the Declaratory Judgment Act is unwarranted. The Court declines to exercise its discretion under the Declaratory Judgment Act over Takeda's § 271(a) infringement claim asserted under the Declaratory Judgment Act. Therefore, the Court dismisses Takeda's Count VII against TWi.

C. Infringement of the '276 Patent

1. Legal Standard on Infringement

393. With the exception of the infringement claim discussed above, Takeda asserts its infringement claims in this action under 35 U.S.C. § 271(e)(2), which provides that:

> [i]t shall be an act of infringement to submit . . . an [ANDA application to the FDA] . . . if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug, veterinary biological product, or biological product claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.

35 U.S.C. § 271(e)(2). "A claim for patent infringement must be proven by a preponderance of the evidence, which simply requires proving that infringement was more likely than not to have occurred." *Warner-Lambert Co. v. Teva Pharm. USA, Inc.*, 418 F.3d 1326, 1348 (Fed. Cir. 2005). An accused product literally infringes the claim if every limitation of the properly construed claim is found in the accused device. *See, e.g., Karlin Tech., Inc. v. Surgical Dynamics, Inc.*, 177 F.3d 968, 971 (Fed. Cir. 1999). Where infringement is asserted under 35 U.S.C. § 271(e)(2)(A) based on the filing of an ANDA, the analysis compares the asserted claims and the product likely to be sold following FDA approval. *Abbott Labs. v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002).

2. Analysis

394. Based on the findings of fact recited above, the Court concludes that Takeda has satisfied its burden of proving by a preponderance of the evidence that Handa's ANDA product contains a crystalline compound of dexlansoprazole and therefore will infringe claims 2 and 3 of the '276 Patent.

395. As discussed above, it is undisputed that Handa's ANDA product contains crystalline material, as reflected in the XRPD peaks at 6.4 and 10.0 degrees two-theta. These peaks cannot be attributed to any of the raw excipients used in the manufacture of the active-layered spheres of Handa's drug product. Further, the Court has found, for the reasons discussed in its Findings of Fact, that the crystal peaks at 6.4 and 10.0 degrees two-theta in the active-layered spheres of Handa's ANDA product are attributable to crystalline dexlansoprazole in Handa's ANDA product.

396. Because the asserted claims cover any crystalline form of dexlansoprazole, the Court finds that Handa's ANDA product infringes claims 2 and 3 the '276 Patent.

D. Validity of Asserted Patents

1. Legal Standards

a. Presumption of Validity

397. Issued patents have a presumption of validity in infringement proceedings. 35 U.S.C. § 282. The party asserting the invalidity of a patent bears the burden of proving invalidity by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd.*, 131 S. Ct. 2238, 2242 (2011). Clear and convincing evidence is such evidence that produces "an abiding conviction that the truth of [the] factual contentions are 'highly probable.'" *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984); *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009).

b. Anticipation

398. Under 35 U.S.C. § 102(a), a patent may be anticipated if the claimed invention was described in a printed publication "before the invention thereof by the applicant for patent." As a general rule, "invalidity by anticipation requires that the four corners of a single, prior art document describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *Advanced Display Systems, Inc. v. Kent State University*, 212 F.3d 1272, 1282 (Fed. Cir. 2000). However, material that is not contained in the single prior art document may be considered where it has been incorporated by reference into that document. *Id.* "Incorporation by reference provides a method for integrating material from various documents into a host document – a patent or printed publication in an anticipation determination – by citing such material in a manner that makes clear that the material is effectively part of the host document as if it were explicitly contained therein." *Id.*

399. "Enablement requires that 'the prior art reference must teach one of ordinary skill in the art to make or carry out the claimed invention without undue experimentation.'" *Elan Pharms., Inc. v. Mayo Found. for Med. Educ. & Research*, 346 F.3d 1051, 1054 (Fed. Cir. 2003) (*quoting Minn. Mining & Mfg. Co. v. Chemque, Inc.*, 303 F.3d 1294, 1301 (Fed. Cir. 2002)). The determination

of what amount of experimentation is considered "undue" for the purposes of determining whether a prior art reference is enabled is made from the point of view of an experienced person in the field of the invention. *Id.* at 1055. Whether a prior art reference is enabling "is a question of law based upon underlying factual findings." *Minn. Mining & Mfg. Co. v. Chemque, Inc.*, 303 F.3d at 1301.

400. To fulfill the enablement requirement, "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention." *Genentech, Inc. v. Novo Nordisk*, 108 F.3d 1361, 1366 (Fed. Cir. 1997).

401. The factors pertinent to enablement under 35 U.S.C. § 112 for patentability are set forth in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). In *Wands*, the Federal Circuit identified the following eight factors that may be pertinent to whether the disclosure of the patent would require undue experimentation:

> (1) the quantity of experimentation necessary,
> (2) the amount of direction or guidance presented,
> (3) the presence or absence of working examples,
> (4) the nature of the invention
> (5) the state of the prior art,
> (6) the relative skill of those in the art,
> (7) the predictability or unpredictability of the art, and
> (8) the breadth of the claim.

Id. at 737. The *Wands* factors are "illustrative, not mandatory" and therefore, the court need consider only the factors that are relevant to the facts of the case. *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991).

402. The *Wands* factors are equally relevant to enablement of prior art. *See Mangosoft, Inc. v. Oracle Corp.*, 421 F. Supp. 2d 392, 405 (D.N.H. 2006) ("[T]he Federal Circuit has also considered the *In re Wands* factors in determining whether a prior art reference is enabling."); *see also Elan Pharms., Inc. v. Mayo Found. for Med. Educ. & Res.*, 346 F.3d 1051, 1054-56 (Fed. Cir. 2003) (considering the *Wands* factors in analyzing enablement of prior art).

403. On summary judgment, the Court found that the burden on the question of enablement, in the context of a challenge to the validity of a patent based on anticipation, falls on the patentee.

See Handa Summary Judgment Order at 35. The Court relied on the Federal Circuit's decision in *In re Antor Media Corp*., 689 F.3d 1282 (Fed. Cir. 2012). In that case, the Federal Circuit held that in the context of patent prosecution, the presumption of enablement applies not only to prior art patents but also to non-patent printed publications. *Id.* at 1288. In its summary judgment order, the Court found that the reasoning of *In re Antor* also applied to anticipation challenges in the district court. The Court now reconsiders its previous conclusion and finds that it is in clear error. *See Willis v. Mullins*, 809 F.Supp.2d 1227, 1232 (E.D. Cal., 2011) (noting that district court has inherent authority to "reconsider and modify an interlocutory decision for any reason it deems sufficient, even in the absence of new evidence or an intervening change in or clarification of controlling law" but that "a court should generally leave a previous decision undisturbed absent a showing that it either represented clear error or would work a manifest injustice.")

404. In *In re Antor*, the Federal Circuit explained that the burden of proving enablement is placed on the patent applicant for reasons of procedural convenience because the applicant "is in a better position to show, by experiment or argument, why the disclosure in question is not enabling or operative." 689 F.3d at 1288. That rationale does not apply, however, in the district court. The court in *Abbot Labs. v. Diamedix Corp*., 969 F. Supp. 1064, 1067-1068 (N.D. Ill. 1997) offered the following reasons for distinguishing between patent prosecution and an invalidity challenge in district court in determining who bears the burden of proving that non-patent prior art is enabling:

> While numerous courts have stated that prior art references are entitled to a presumption of enablement . . ., these courts have each relied incorrectly upon *In re Sasse*, 629 F.2d 675, 681 (C.C.P.A. 1980) for the proposition that the patent holder bears the burden of proving that prior art references are not enabling. In *Sasse*, the court was faced with an appeal from a PTO Board of Appeals decision affirming the rejection of certain patent claims. In such a situation, where the applicant has not yet received a patent, it is clearly up to the applicant to prove to the PTO that he or she is entitled to one. Thus, once the PTO cites a prior art reference that enjoys a presumption of enablement, the burden shifts to the applicant. However, in the present case, unlike *Sasse*, the patents in question themselves have a presumption of validity. Since the burden is always on the challenger to show invalidity by clear and convincing evidence, *Jervis B. Webb Co. v. Southern Sys*., 742 F.2d 1388, 1392 (Fed. Cir. 1984) ("Regardless of the prior art introduced by the party asserting invalidity, the presumption [of validity] remains intact."); *Oak Indus., Inc. v. Zenith Elec. Corp*., 726 F. Supp. 1525, 1530 (N.D. Ill. 1989) ("This clear and convincing standard applies even

> though the prior art introduced in court was not considered by the PTO."), once [the accused infringer] has shown that each and every claim is cited in [a cited prior art] reference, i.e., identity, [the patentee] only has the burden of producing some material evidence which places the enablement of the reference in question. Once it has done so, [the accused infringer] must show by clear and convincing evidence that the [the] reference was, in fact, enabling.

Id.; *see also Jacobs Vehicle Equip. Co. v. Pac. Diesel Brake Co.*, 829 F. Supp. 2d 11, 33 (D. Conn. 2011) (finding the reasoning of *Diamedix* persuasive and holding that in the context of an anticipation challenge in district court, the burden is on the alleged infringer to prove by clear and convincing evidence that prior art is enabled)

405. While *Diamedix* and *Jacobs* were decided before the Federal Circuit issued its decision in *In re Antor*, the Court finds that the reasoning in those cases persuasive and therefore, that the Federal Circuit would not extend the holding of *In re Antor* to challenges based on anticipation that are being litigated in the district court. *See* 1 Donald S. Chisum, *Chisum on Patents* § 3.04(1)(b)(v) (2011) (relying, in part, on *Diamedix* and opining, "It is likely that the Federal Circuit will apply [the following approach] to the issue of the enabling quality of a prior art reference": "If a challenger provides evidence sufficient to establish a prima facie showing on an issue, the burden of production of evidence shifts to the patent owner. If the patent owner provides some contradictory evidence, then the trier of fact must resolve the conflict with the challenger, as noted, bearing the burden of persuasion by clear and convincing evidence").

406. For the reasons stated above, the Court concludes that the ultimate burden of proving enablement of non-patent prior art that is alleged to anticipate is on the party that is challenging the validity of the patent, who must establish enablement by clear and convincing evidence.

c. Obviousness

407. Obviousness under 35 U.S.C. § 103 is a question of law based on factual underpinnings. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). To invalidate a patent claim based on obviousness, a challenger must demonstrate "by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Procter & Gamble v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir.

2009) (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007)).

408. Analogous prior art is considered when evaluating obviousness. *See Wang Labs., Inc. v. Toshiba Corp.*, 993 F.2d 858, 863-64 (Fed. Cir. 1993). The Federal Circuit in *Wang* explained:

> Two criteria are relevant in determining whether prior art is analogous: (1) whether the art is from the same field of endeavor, regardless of the problem addressed, and (2) if the art is not within the same field of endeavor, whether it is still reasonably pertinent to the particular problem to be solved.

Id. at 864 (internal citation omitted). These are factual issues. *See Finish Eng'g Co. v. Zerpa Indus., Inc.*, 806 F. 2d 1041, 1043-44 (Fed. Cir. 1986).

409. Whether the claimed invention is obvious must be evaluated from the perspective of a hypothetical person of ordinary skill in the art. *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 666 (Fed. Cir. 2000). In determining what constitutes ordinary skill in the art, a court may consider "(1) the types of problems encountered in the art; (2) the prior art solutions to those problems; (3) the rapidity with which innovations are made; (4) the sophistication of the technology; and (5) the educational level of active workers in the field." *Id.* at 666-667. The hypothetical person of ordinary skill in the art is presumed to be aware of all analogous prior art. *In re Gorman*, 933 F.2d 982, 986 (Fed. Cir. 1991).

410. The obviousness determination turns on underlying factual inquiries involving: (1) the scope and content of prior art, (2) differences between claims and prior art, (3) the level of ordinary skill in pertinent art, and (4) evidence of secondary factors, such as long-felt need and failure by others, unexpected results, or commercial success. *Graham*, 383 U.S. at 17; *Texas Instruments, Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993). However, the absence of secondary considerations does not prove obviousness. *See Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 960 (Fed. Cir. 1986) ("[T]he absence of objective evidence [of commercial success, longfelt but unresolved need, failure of others, or copying] does not preclude a holding of nonobviousness because such evidence is not a requirement for patentability. . . . [T]he absence of objective evidence is a neutral factor" (quotations omitted)); *see also Miles Labs., Inc. v. Shandon Inc.*, 997 F.2d 870, 878 (Fed. Cir. 1993) ("[The patent owner] did not show objective indicia of non-obviousness. Such evidence, if

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present, would weigh in favor of non-obviousness, although the lack of such evidence does not weigh in favor of obviousness.").

411. A factor to be considered in determining obviousness is whether a prior art reference "teaches away" from the claimed invention. *Depuy Spine, Inc. v. Medtronic Sofamor Danek*, Inc., 567 F.3d 1314, 1326 (Fed. Cir. 2009). "A reference will teach away when it suggests that the developments flowing from its disclosures are unlikely to produce the objective of the applicant's invention." *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005) (citation omitted).

412. "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). However, obviousness is not established "merely by demonstrating that each of [an invention's] elements was . . . known in the prior art," because "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR*, 550 U.S. at 418; *see* also *Ruiz*, 234 F.3d at 665 ("[T]he notion that combination claims can be declared invalid merely upon finding similar elements in separate prior patents would necessarily destroy virtually all patents and cannot be the law under the statute, § 103").

413. The Federal Circuit has explained that:

> A suggestion, teaching, or motivation to combine the relevant prior art teachings does not have to be found explicitly in the prior art, as the teaching, motivation, or suggestion may be implicit from the prior art as a whole, rather than expressly stated in the references.... The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art.

In re Kahn, 441 F.3d 977, 987-88 (Fed. Cir. 2006) (quoting *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000)).

414. Claimed subject matter may be obvious when it might have been obvious to try known options within the technical grasp of the ordinarily skilled person, but only when there is "a design need or market pressure to solve a problem and there are a finite number of identified, predictable

solutions." *KSR*, 550 U.S. at 421.

415. When relying on a "combination" of references, "the burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, and would have had a reasonable expectation of success in doing so." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007) (citations omitted). The purpose of this requirement is to "prevent hindsight bias." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1164 (Fed. Cir. 2006). "In making obviousness determinations, the test is 'whether the subject matter of the claimed inventions would have been obvious to one skilled in the art at the time the inventions were made, not what would be obvious to a judge after reading the patents in suit and hearing the testimony.'" *Id.* (quoting *Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082, 1092 (Fed. Cir. 1985).

d. Written Description

416. 35 U.S.C. § 112 states:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out his invention.

417. Lack of an adequate written description must be established by the challenger by clear and convincing evidence. *ICU Med., Inc. v. Alaris Med. Sys., Inc.*, 558 F.3d 1368, 1376 (Fed. Cir. 2009). The written description requirement is met where the disclosure reasonably conveys to those of ordinary skill in the art that the inventor had possession of the claimed subject matter as of the filing date. *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). The written description requirement is distinct from the enablement requirement, although the two "often rise and fall together." *Id.* at 1352.

418. To satisfy the written description requirement, "the applicant does not have to utilize any particular form of disclosure to describe the subject matter claimed, but the description must clearly allow persons of ordinary skill in the art to recognize that he or she invented what is

claimed." *Carnegie Mellon Univ. v. Hoffman-La Roche, Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008). Put differently, "the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention . . . and demonstrate that by disclosure in the specification of the patent." *Id.* at 1122. So long as these requirements are met, "[the applicant] does not have to describe exactly the subject matter claimed." *In re Hayes Microcomputer Prods., Inc. Patent Litig.*, 982 F.2d 1527, 1533 (Fed. Cir. 1992). "[I]t is unnecessary to spell out every detail of the invention in the specification" to satisfy the written description requirement, *LizardTech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005), and the written description requirement does not "require a re-description of what was already known." *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005). Instead, "[t]he descriptive text needed to meet [the] requirement varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence." *Id.*

2. Whether the Crystal Form Patents are Obvious

a. Claims 1 and 3 of the '058 Patent[7]

419. Based on the findings of fact recited above, the Court concludes that claims 1 and 3 of the '058 Patent are not obvious over the disclosures of Larsson, Von Unge, or Barberich in view of Kato, Nohara, Kohl, Bohlin, Tietze, Vogel, or Gordon.

420. The Court further concludes that claims 1 and 3 of the '058 Patent are not obvious over the disclosures of Katsuki, Tanaka, Borner and Erlandsson in view of Kato, Nohara, Kohl, Bohlin, Tietze, Vogel, or Gordon.

421. Although the Court has found that a person of ordinary skill in the art would have had a reason to try to crystallize the R enantiomer of lansoprazole, Defendants have not presented clear and convincing evidence that such a person would have had a reasonable expectation of being able successfully to synthesize crystalline dexlansoprazole in light of the prior art cited by Defendants

[7] Takeda asks the Court to find, as a matter of law, that Barberich II is not prior art to the '058 Patent. Because the Court reaches the same result as to the validity of the '058 Patent regardless of whether or not Barberich II is prior art, it assumes that Barberich II is prior art to that patent but does not decide this issue.

for the reasons stated in the Court's Findings of Facts.

422. First, as discussed above, a person of ordinary skill in the art would not have had a reasonable expectation of being able successfully to synthesize crystalline dexlansoprazole in light of the disclosures of Larsson and Von Unge, which disclosed the failure to obtain dexlansoprazole in crystalline form. In particular, Larsson and Von Unge disclosed the production of a very pure sample of dexlansoprazole in oil form, which would have suggested to a person of skill in the art that impurities in the sample were not responsible for the failure of crystallization and that the material might not exist in crystal form at room temperature. In this way, Larsson and Von Unge teach away from dexlansoprazole in crystal form. Likewise, as explained above, because the Barberich reference is devoid of any mention, much less any enabling disclosure, of a crystal of dexlansoprazole, it does not, alone or in combination with other prior art, render crystalline dexlansoprazole obvious. At most, Impax and Handa have merely presented evidence that it would have been obvious to try to make all possible forms of dexlansoprazole and its enantiomers, including crystalline forms. This does not suffice to establish obviousness. As discussed above, in *KSR*, the Supreme Court held that a showing that the prior art rendered a combination obvious to try alone might be sufficient to prove obviousness "[w]hen there is a design need or market pressure to solve a problem and there are a *finite number of identified, predictable solutions*" that leads to an anticipation of success. 550 U.S. at 421 (emphasis added). This is not the case here. Rather than a "finite number of identified, predictable solutions," there were myriad possible solvents, combinations of solvents, and adjustment of conditions (e.g., time and temperature) that could have been used to attempt to crystallize dexlansoprazole.

423. Moreover, as discussed above, crystallization of benzimidazole compounds such as dexlansoprazole is unpredictable, as evidenced by the various methods and solvent combinations disclosed in the prior art references to treat other benzimidazole compounds, and the different forms of matter – amorphous solids, crystalline solids, partially crystalline solids, hydrates, ethanolates, and oils – obtained through such methods. Dr. Genck admitted that even he could not predict *a priori* whether any given solvent or solvent combination would lead to crystallization of dexlansoprazole. Rather, a skilled artisan would have to try each of numerous possibilities in

terms of solvents, solvent combinations, and/or conditions until possibly arriving at a successful result. Thus, the record does not contain a finite number of identified, predictable solutions which would support a finding of obviousness. *See Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008) ("To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on [ ] 'identified, predictable solutions' may present a difficult hurdle [for patent challengers] because potential solutions are less likely to be genuinely predictable."); *see also In re Brimonidine Patent Litig.*, 643 F.3d 1366, 1376 (Fed. Cir. 2011) (rejecting "obvious to try" argument based on district court's finding that prior art suggested "roadblocks" such that the claimed invention would not have been an expected result); *In re Armodafinil Patent Litig.* ('722 Patent Litigation), 2013 WL 1332523, at *39 (D. Del. Mar. 30, 2013) ("the Federal Circuit has clarified that 'obvious to try' is also not obvious when a skilled artisan would have to: (1) 'vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave . . . no direction as to which of many possible choices is likely to be successful; or (2) explore a new technology or general approach that seemed to be a promising [field] of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.'") (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988) and citing *In re Kubin*, 561 F.3d 1351, 1359-60 (Fed. Cir. 2009) (reaffirming holdings in *O'Farrell* in view of *KSR*)); *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1072-73 (Fed. Cir. 2012) ("Evidence of obviousness, especially when that evidence is proffered in support of an 'obvious-to-try' theory, is insufficient unless it indicates that the possible options skilled artisans would have encountered were 'finite,' 'small,' or 'easily traversed,' and that skilled artisans would have had a reason to select the route that produced the claimed invention.").

424. The Court rejects Impax's argument that the anhydrous crystal of claim 1 of the '058 Patent and claim 7 of the '971 Patent is obvious because the crystallization techniques used to make it are obvious. The last sentence of the statutory section on obviousness applicable to the patents-in-suit, 35 U.S.C. § 103(a), states that "[p]atentability shall not be negated by the manner

in which the invention was made."[8] "[E]ven assuming that there would have been a motivation to obtain the 'most stable' form of [a compound], a skilled artisan would have expected to resort to trial and error experimentation, using a large number of conditions, to try to make this form." *Armodafinil*, 2013 WL 1332523 at *34.

425. Dr. Genck similarly applied an incorrect test for obviousness when he concluded that crystalline dexlansoprazole would be obvious because the methods used to obtain it would be obvious. *See* Trial Tr. (Genck Cross) 802:10-15. The proper question with respect to these claims is whether the patented subject matter itself, not the method by which it was made, is obvious. *See Zenith Labs., Inc. v. Bristol-Myers Squibb Co.*, 19 F.3d 1418, 1422 (Fed. Cir. 1994) (holding that the patentability of a claim directed to a chemical compound "derives from the structure of the claimed compound in relation to prior compounds"); *In re Certain Crystalline Cefadroxil Monohydrate*, 15 U.S.P.Q.2d 1263, 1270 (U.S.I.T.C. 1990) ("The patentability of a new chemical structure is independent of how it is made") (quoting *Bristol-Myers Co. v. USITC*, 15 U.S.P.Q.2d 1258, 1262 (Fed. Cir. 1989) (unpublished opinion). Thus, in *In re Cofer*, 354 F.2d 664 (C.C.P.A. 1966), the Court of Customs and Patent Appeals held that the Board of Appeals, in finding obvious claims to a crystalline form of a compound previously known to exist in liquid form, erred by failing to consider "whether the prior art suggests the particular structure or form of the compound or composition as well as suitable methods of obtaining that structure or form." *Id.* at 666-668.

426. Defendants have identified no evidence that disclosed or suggested the structure of the specific anhydrous crystalline form described in claim 1 of the '058 Patent or any crystalline form of dexlansoprazole prior to Takeda's invention. Nor have Defendants pointed to any evidence indicating that one would reasonably expect that specific crystalline compound to result from any prior art. As a result, Dr. Genck's reliance on the fact that the inventors used known methods is misplaced.

427. *In re Irani*, 427 F.2d 806 (C.C.P.A. 1970) also supports the Court's conclusion. There, the

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[8] Prior to its amendment in 2011, the last sentence of § 103 used the word "negative" rather than "negated".

Court of Customs and Patent Appeals found a claim for an anhydrous crystal of a compound previously known to exist in amorphous form to be patentable and nonobvious over prior art disclosing the crystallization of some related compounds. *Id.* at 809. The court noted that, "[t]he most definite conclusion that can be reached is that some of these [compounds] can be obtained in crystalline form and some cannot. . . . ," and that the prior art disclosure "would not provide a basis for predicting with reasonable certainty that [the compound] could exist in a crystalline anhydrous form." As in *Irani*, the prior art here discloses some benzimidazole compounds in crystalline form but others in amorphous solid or oil form. As discussed above, Larsson shows the isolation of enantiomers of some benzimidazole compounds in crystal form, others as amorphous solids, and others as oils. As in *Irani*, comparisons to related compounds in the prior art do not demonstrate that one would have an expectation of being able to make crystalline dexlansoprazole prior to the work of the Takeda inventors.

428. Likewise, the Court rejects Defendants' argument that the relatively short amount of time it took Dr. Kamiyama to invent the claimed dexlansoprazole crystal supports their position that his invention was obvious. This is not a relevant consideration for determining whether an invention is obvious. *See Shiley, Inc. v. Bentley Laboratories, Inc.*, 794 F.2d 1561, 1568 (Fed. Cir. 1986) (obviousness not established by speed with which inventor conceived the successful design because "the patentability of an invention does not depend on how the invention is made").

429. The Court finds distinguishable the Federal Circuit's opinion in *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007), upon which Defendants rely in support of their argument that an invention may be obvious, even though some experimentation is required, if it uses a known process. In that case, the Federal Circuit held that certain claims covering the besylate salt of a known compound would have been obvious because the prior art included a reference that disclosed a genus of pharmaceutically acceptable anions that could be used to form pharmaceutically acceptable acid addition salts, as well as other publications that disclosed the chemical characteristics of the besylate salt form in general. *Id.* at 1363. Thus, "on the particularized facts" of the case, the Federal Circuit found that "consideration of the 'routine testing' performed by Pfizer [was] appropriate because the prior art provided not only the means

of creating acid addition salts but also predicted the results, which Pfizer merely had to verify through routine testing." *Id.* at 1367.

430. The critical distinction is that both the method of making the salt claimed in *Pfizer*, and the structure of that salt, which merely consisted of a pharmaceutically acceptable acid reacted with the neutral compound, were predictable and known at the time of the claimed invention. Here, the three-dimensional structure that is the critical aspect of the claimed crystalline dexlansoprazole was neither known nor predictable at the time of the invention. *See Armodafinil*, 2013 WL 1332523 at *28 (finding that "[u]nlike salts, which for the most part can be prophetically claimed based on an understanding of the chemical structure of the compound and its ionization constants, the existence and identity of . . . polymorphs have defied prediction"). Whereas *Pfizer* involved the selection of which particular salt to make from among a known, predictable and limited universe of salts, here the invention involved the selection from a broad range of available but unpredictable techniques to try to create a previously non-existent crystalline compound whose structure could not be predicted.

431. The Court concludes that Impax's argument that the particular crystal defined in claim 1 of the '058 Patent would have been obvious is based on hindsight analysis. Only with the teachings of the '058 Patent are the d-spacings, and thus, the physical three-dimensional structure, of that crystal known. Accordingly, the crystal of claim 1 is not obvious. For the same reasons, the pharmaceutical composition of such a crystal, described in claim 3, also is not obvious.

b. Claims 2 and 3 of the '276 Patent

432. Based on the findings of fact recited above, the Court concludes that claims 2 and 3 of the '276 Patent also are not obvious in view of the prior art. As discussed above, Dr. Genck testified that the basis for his opinion that the '276 Patent is not valid is the same as that of his opinion with respect to the '058 Patent. With the exception of the findings and analysis specifically relating to the uniqueness and unpredictability of the particular anhydrous polymorph defined in claim 1 of the '058 Patent, the preceding findings and analysis apply to the claims of the '276 Patent as well. The fact that potential methods of attempting crystallization were known at the time of the invention does not render the crystals invented by Takeda obvious given the acknowledged

unpredictability of crystallization techniques, the absence of any teaching that would tell one skilled in the art which particular crystallization technique to try to crystallize dexlansoprazole, and the teaching of Larsson and Von Unge, which indicated that dexlansoprazole in very pure form existed as an non-crystalline oil.

433. Likewise, the references relied on by Dr. Genck relating to HPLC would not teach one of ordinary skill in the art how to make dexlansoprazole for the purposes of crystallization. As discussed above, these references fail to describe certain steps in the preparation of dexlansoprazole that were done to overcome challenges in synthesizing material appropriate for crystallization in the preparation of the material used for the successful crystallization of dexlansoprazole set forth in the '058 Patent. Moreover, even if one of ordinary skill in the art would have been motivated to obtain dexlansoprazole using HPLC for the purposes of performing crystallization, such a person would not have had a reasonable expectation of success in obtaining crystals, as discussed above.

434. Just as the specific crystal form of dexlansoprazole claimed in the '058 Patent was unknown and unpredictable before Takeda's invention, no crystalline form of dexlansoprazole was known or predictable prior to the Takeda patents. Indeed, the prior art taught away from dexlansoprazole crystals, as discussed above. Defendants have identified no evidence that disclosed or suggested the structure of any crystalline form of dexlansoprazole or that any such crystal would or should be made by any prior art process. Indeed, as discussed above, the prior art showed that crystallization of benzimidazole compounds is unpredictable and taught away from the existence of dexlansoprazole in crystal form. Defendants here, as in *Cofer*, failed to introduce evidence of "whether the prior art suggests the particular structure or form of the compound or composition *as well as* suitable methods of obtaining that structure or form." 354 F.2d at 666-668 (emphasis added). And as in *Armodafinil*, a person of ordinary skill in the art would not have known of the existence of dexlansoprazole in crystal form and could not have reasonably expected to produce it with any particular solvent prior to the teachings of the Takeda patents.

c. Claims 6 and 7 of the '971 Patent

435. Based on the findings of fact recited above, and for the same reasons set forth above in

connection with claim 3 of the '276 Patent and claim 3 of the '058 Patent, the Court finds that claims 6 and 7 of the '971 Patent are not obvious in view of the prior art.

3. Whether Claims 1 and 2 of the '282 Patent are Anticipated

a. Whether Barberich II Anticipates an Amorphous Compound of Dexlansoprazole

436. As discussed above, Handa and TWi contend that claims 1 and 2 of the '282 Patent are anticipated by the Barberich II. The Court concludes that Barberich II does not anticipate claims 1 and 2 of the '282 Patent, despite its disclosure of solid pharmaceutical compositions of dexlansoprazole, because the person of ordinary skill would not have been able to make the amorphous solid of dexlansoprazole described by Barberich without undue experimentation.

437. Barberich purports to disclose a solid pharmaceutical composition of dexlansoprazole. The parties agree that a skilled person already in possession of the amorphous solid of dexlansoprazole disclosed in the '282 Patent would have understood from prior art such as Larsson how to make a solid dosage form without undue experimentation. *See, e.g.,* Trial Tr. (Rogers Direct) 547:23-548:9 (testifying that Example 1 of Barberich II, TX 0078-0005, would not require undue experimentation because "[e]ssentially this is a recipe"); *id.* (Rogers Direct) 575:12-576:4 (testifying that Larsson, which predates Barberich, discloses the "pharmaceutically acceptable excipient, carrier, or diluent limitation of claim 2 of the '282 Patent"). Thus, to the extent it contains anything novel, Barberich's novelty is its disclosure of a solid form of dexlansoprazole. Consequently, to satisfy the enablement requirement, Barberich must disclose a method for synthesizing a solid form of dexlansoprazole . *See Genentech*, 108 F.3d at 1366.

438. Consideration of the evidence relevant to the *Wands* factors persuades the Court that Barberich (including the disclosures of Larsson that are incorporated by reference in Barberich) would not have enabled the person of ordinary skill to make the amorphous solid of dexlansoprazole described by Barberich without undue experimentation.

439. **The Amount of Direction or Guidance Provided by the Specification:** Barberich merely incorporates by reference the synthesis methods disclosed in Larsson and Von Unge. *See* TX 0078 (Barberich II) at [0013]. However, as discussed above, Larsson discloses the synthesis

only of an oily form of dexlansoprazole; it does not describe any process for converting that oil to a solid. Similarly, the Barberich specification provides no direction or guidance as to how to convert the oil in Larsson into a solid.

440. **The Presence or Absence of Working Examples Set Forth in the Specification**: The Barberich specification does not contain any working examples regarding how to synthesize solid dexlansoprazole. Instead, all of the examples in Barberich that describe solid dexlansoprazole are set forth in present tense, indicating that they are "prophetic" and were not carried out. *See Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1376 n. 1 (Fed. Cir. 2003)("Prophetic examples are set forth in the present tense to indicate that they were not carried out") (citing *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1578 (Fed.Cir.1984)). There is no evidence that Barberich ever actually obtained the solid. Similarly, the subject matter of Larsson and Von Unge that is incorporated by reference in Barberich II does not set forth any working example showing how to synthesize solid dexlansoprazole.

441. **Nature of the Invention and the Relative Skill of a Person of Ordinary Skill in the Art**: The invention of Barberich II is a pharmaceutical formulation of dexlansoprazole. Accordingly, the level of skill of the person of ordinary skill in the art of the Barberich invention would be a formulator with a bachelor's degree in pharmacy or a related field, with three to five of experience in pharmaceutical formulations. The person of ordinary skill would also need to understand some organic chemistry because of Barberich's incorporation of the Larsson and Von Unge references, but this person's focus would be formulation.

442. **The State of the Prior Art**: As discussed above, the Larsson and Von Unge references are the closest prior art references and are incorporated into Larsson. Neither Larsson nor Von Unge discloses the synthesis of a solid form of dexlansoprazole.

443. **Predictability or Unpredictability of the Art**: The synthesis of solid dexlansoprazole, which falls within the field of organic chemistry, is unpredictable. *See Boston Scientific v. Johnson & Johnson*, 679 F. Supp.2d 539, 557 (D. Del. 2010) (noting that "the chemical arts have long been acknowledged to be unpredictable"). Organic chemistry is an experimental science, meaning that one cannot predict the outcome of an experiment without actually carrying out the

experiment (such as a crystallization or synthesis) in the laboratory. *See* Trial Tr. (Atwood Direct) 903:20-905:5; *Application of Carleton*, 599 F.2d 1021, 1026 (Cust. & Pat. App. 1979) ("Although there is a vast amount of knowledge about general relationships in the chemical arts, chemistry is still largely empirical, and there is often great difficulty in predicting precisely how a given compound will behave"); *Schering Corp. v. Gilbert*, 153 F.2d 428, 433 (2d Cir. 1946) ("Organic chemistry is essentially an experimental science and results are often uncertain, unpredictable and unexpected").

444. **The Breadth of the Claim**: Barberich states that its pharmaceutical formulations can take either solid or liquid form. The person of ordinary skill could have used the oil of dexlansoprazole disclosed in Larsson to make a liquid formulation of dexlansoprazole that would have fallen within the scope of the Barberich claims. *See* TX 0078-0004 (Barberich II) at [0034] ("Pharmaceutical compositions of the present invention suitable for oral administration may be presented as . . . an oil-in-water emulsion, or a water-in-oil liquid emulsion."); Trial Tr. (Rogers Cross) 618:22-619:6 ("I think if dexlansoprazole was an oil, then you could incorporate that into an emulsion, along with whatever solvent was with it.").

445. **The Quantity of Experimentation Needed**: The experiments performed at the University of Wisconsin under the direction of Dr. Elder demonstrate that the person of ordinary skill would not have been able to make solid amorphous dexlansoprazole based on the disclosures of Barberich without considerable and undue experimentation.

446. Dr. Elder attempted to replicate Example 22 two times, and both times he failed to obtain the oil Larsson describes. The first experiment, in which Dr. Elder opted for a "literal interpretation of Larsson," Trial Tr. (Rogers Direct) 513:3-10, resulted in a solid of "nearly racemic" lansoprazole, with only a "slight preference" (6% e.e.) for dexlansoprazole. TX 0733x03-0004-5 and -0008 (UW Report). In the second experiment, Dr. Elder departed from the teachings of Larsson by adding the 1.1 milliliters of oxidant over a 60-minute period instead of in one portion. However, Larsson teaches that good enantioselectivity in the asymmetric oxidation process does not require reduced temperatures but can be conducted at or above room temperature. *See* TX 301-0005, col.8, ll.44-47; *see also* Trial Tr. (Atwood Direct) 911:4-912:19; *id.* (Rogers

Cross) 638:14-639:2, 651:3-7 ("[O]ne of [Larsson's] big advances was to be able to do this [oxidation reactions] at room temperature or above"). Larsson itself would have provided the most up-to-date disclosure regarding how to add the oxidant in an asymmetric oxidation reaction for the person of ordinary skill attempting to replicate Example 22 of Larsson in 1998 (the priority date of the Barberich reference) or 1999 (the priority date of the '282 Patent). *See* Trial Tr. (Atwood Direct) 911:4-14; cf. Trial Tr. (Rogers Cross) 635:15-637:6. Because slowing down the rate of oxidant addition is an alternative to simply lowering the temperature of the reaction, the person of ordinary skill would have concluded from this teaching in Larsson that dropwise addition of 1.1 milliliters of oxidant over 60 minutes would not be a way of obtaining improved enantioselectivity. Trial Tr. (Atwood Direct) 911:4-913:7.

447. Dr. Elder's selection of the solvents used during the workup procedures and the ratios for the flash chromatography gradient also would not have been a matter of routine experimentation for the person of ordinary skill implementing Example 22, but, instead, were informed by the subsequent evolution of the art.

448. Because of these departures from the teachings of Larsson, Dr. Elder obtained a solid from the workup procedure – in fact, Dr. Elder never obtained an oil of dexlansoprazole. Because Dr. Elder never obtained an oil of dexlansoprazole, in contrast to the explicit teachings of Larsson, UW's experiments fail to establish that the oil obtained by Larsson could have been evaporated to dryness to obtain a solid.

449. In addition, the chemical purity of the "light, brown solid" obtained by Dr. Elder following the workup procedures is unknown and unreported, as the UW lab failed to assess its chemical purity using achiral HPLC.

450. For all of these reasons, the experiments performed at UW do not indicate that one skilled in the art could have converted that oil into an amorphous solid. Instead, with the benefit of hindsight knowledge that a solid amorphous dexlansoprazole compound could be obtained, Dr. Elder conducted an experiment different from that described in Larsson and different from how the ordinarily skilled person in 1998 would have attempted to adapt the Larsson reference to obtain a solid.

451. Based on the foregoing analysis of the *Wands* factors, the Court concludes that Barberich would not have enabled the person of ordinary skill at the relevant time to make the amorphous solid of dexlansoprazole described by Barberich without undue experimentation.[9]

b. Whether Barberich II Anticipates an Amorphous Salt of Dexlansoprazole

452. As discussed above, in its Findings of Fact, the Court finds that Handa and TWi failed to establish by clear and convincing evidence that a person of skill in the art could have obtained an amorphous solid salt of dexlansoprazole from the oil obtained in Larsson and incorporated by reference in Barberich II. Further, for the reasons discussed above, to obtain the solid form of amorphous dexlansoprazole disclosed in Barberich from which a solid salt could be derived would require undue experimentation.

4. Whether Claims 1 and 2 of the '282 Patent are Obvious

453. Based on the findings of fact recited above, the Court concludes that it would not have been obvious for one ordinarily skilled in the art in 1999 to evaporate the oil described in Larsson and Von Unge (and incorporated by reference in Barberich) using known techniques to obtain an amorphous solid. In particular, although a person of ordinary skill in the art would have been motivated to obtain an amorphous solid form of dexlansoprazole, such a person would not have had a reasonable expectation of success based on this prior art.

454. Similarly, based on the findings of fact recited above, the Court concludes that claim 1 of the '282 Patent is not obvious in view of Larsson, Von Unge, or Barberich II in combination with Takechi, Brittain, and/or Bohlin because a person of ordinary skill in the art also would not have had a reasonable expectation of success in obtaining an amorphous solid of dexlansoprazole based on this prior art.

455. Finally, Claim 2 of the '282 Patent also is not obvious in view of Larsson or Von Unge in

[9] Although the Court has found that it is the burden of Handa and TWi to establish by clear and convincing evidence that Barberich is enabling – and that Handa and TWi have failed to meet that burden – the Court notes that even if the burden fell on Takeda to establish by the preponderance of the evidence that Barberich is *not* enabled, the evidence presented at trial was sufficient to meet that burden.

combination with Barberich, the PDR entry for Prevacid, and/or Katsuki for the same reason.

5. Whether Claims 1 and 2 of the '282 Patent Satisfy the Written Description Requirement

456. Based on the findings of fact recited above, the Court concludes that the person or ordinary skill reviewing Reference Examples 1 and 2 of the '282 Patent would have understood that the inventors were in possession of an amorphous solid of dexlansoprazole.

457. Defendants contend that claim 1 of the '282 Patent is invalid for failure to satisfy the written description requirement because the specification describes crystalline compounds of dexlansoprazole as its invention. That the specification does not place as much emphasis on the amorphous form of dexlansoprazole as it does on the crystal form is of no import. As the Federal Circuit has recognized, to satisfy the written description requirement, "the applicant does not have to utilize any particular form of disclosure to describe the subject matter claimed, but the description must clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *Carnegie*, 541 F.3d at 1122. Put differently, "the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention . . . and demonstrate that by disclosure in the specification of the patent." *Id.*

458. These requirements are met here. The description of the isolation of amorphous solid dexlansoprazole in the specification clearly demonstrates that the inventors of the '282 Patent were in possession of that compound, and that a person of ordinary skill in the art could recognize that they were in possession of the subject matter of claim 1.

IV. CONCLUSION

459. For all of the foregoing reasons, the Court concludes that: (1) TPC, TPNA, Takeda LLC, and TPA each have sufficient exclusive right to the asserted patents to have standing to assert these patents; (2) Handa infringes the '276 Patent; (3) the asserted claims of the '058, '276, and '971 Patents are valid; and (4) the asserted claims of the '282 Patent are valid. The Court declines to exercise declaratory judgment jurisdiction over TWi's claim under 35 U.S.C. § 271(a) and the Declaratory Judgment Act.

460. Takeda is ordered to submit a proposed judgment incorporating the rulings contained in this opinion.

IT IS SO ORDERED.

Dated: October 17, 2013

JOSEPH C. SPERO
United States Magistrate Judge

United States District Court
Northern District of California

UNITED STATES DISTRICT COURT

FOR THE

NORTHERN DISTRICT OF CALIFORNIA

TAKEDA PHARMACEUTICAL CO., LTD
ET AL et al,

Plaintiff,

v.

HANDA PHARMACEUTICALS, LLC et al,

Defendant.
_______________________________/

Case Number: CV11-00840 JCS
CV11-1609 JCS
CV11-1610 JCS

[redacted] **CERTIFICATE OF SERVICE**

I, the undersigned, hereby certify that I am an employee in the Office of the Clerk, U.S. District Court, Northern District of California.

That on October 17, 2013, I SERVED a true and correct copy(ies) of the attached, by placing said copy(ies) in a postage paid envelope addressed to the person(s) hereinafter listed, by depositing said envelope in the U.S. Mail, or by placing said copy(ies) into an inter-office delivery receptacle located in the Clerk's office.

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